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(71) Applicant *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: WEI, Dong, D. [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). WILLIAMS, Theresa, M. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(54) Title: INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

(57) Abstract

The present invention is directed to compounds which inhibit farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for inhibiting farnesyl-protein transferase and the farnesylation of the oncogene protein Ras.

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TITLE OF THE INVENTION

INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

BACKGROUND OF THE INVENTION

The Ras proteins (Ha-Ras, Ki4a-Ras, Ki4b-Ras and N-Ras) are part of a signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon growth factor receptor activation Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, *Ann. Rev. Biochem. 62*:851-891 (1993)). Mutated *ras* genes (Ha-*ras*, Ki4a-*ras*, Ki4b-*ras* and N-*ras*) are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory signal.

Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa^1-Aaa^2-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al., Nature 310*:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C_{15} or C_{20} isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem. 61*:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics 30*:209-237 (1992)). The Ras protein is one of several proteins that are known to undergo post-translational

farnesylation. Other farnesylated proteins include the Ras-related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem. 269*, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Inhibition of farnesyl-protein transferase has been shown to block the growth of Ras-transformed cells in soft agar and to modify other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl *et al., Science, 260*:1934-1937 (1993) and G.L. James *et al., Science, 260*:1937-1942 (1993). Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of *ras*-dependent tumors in nude mice (N.E. Kohl *et al., Proc. Natl. Acad. Sci U.S.A., 91*:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl *et al., Nature Medicine*, 1:792-797 (1995).

Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock *et al., ibid*; Casey *et al., ibid*; Schafer *et al., Science 245*:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including farnesyl pyrophosphate. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss *et al., Cell, 62*:81-88 (1990); Schaber *et al.. J. Biol. Chem., 265*:14701-14704 (1990); Schafer *et al., Science, 249*:1133-1139 (1990); Manne *et al., Proc. Natl. Acad. Sci USA, 87*:7541-7545 (1990)). Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells. However, direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side

effects than would occur with the required dose of a general inhibitor of isoprene biosynthesis.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first are analogs of farnesyl diphosphate (FPP), while the second class of inhibitors is related to the protein substrates (e.g., Ras) for the enzyme. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al.*, *ibid*; Reiss *et. al.*, *ibid*; Reiss *et al.*, *PNAS*, *88*:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al.*, *Science*, *260*:1934-1937 (1993); Graham, et al., *J. Med. Chem.*, *37*, 725 (1994)). In general, deletion of the thiol from a CAAX derivative has been shown to dramatically reduce the inhibitory potency of the compound. However, the thiol group potentially places limitations on the therapeutic application of FPTase inhibitors with respect to pharmacokinetics, pharmacodynamics and toxicity. Therefore, a functional replacement for the thiol is desirable.

It has recently been reported that farnesyl-protein transferase inhibitors are inhibitors of proliferation of vascular smooth muscle cells and are therefore useful in the prevention and therapy of arteriosclerosis and diabetic disturbance of blood vessels (JP H7-112930).

It has recently been disclosed that certain tricyclic compounds which optionally incorporate a piperidine moiety are inhibitors of FPTase (WO 95/10514, WO 95/10515 and WO 95/10516). Imidazole-containing inhibitors of farnesyl protein transferase have also been disclosed (WO 95/09001 and EP 0 675 112 A1).

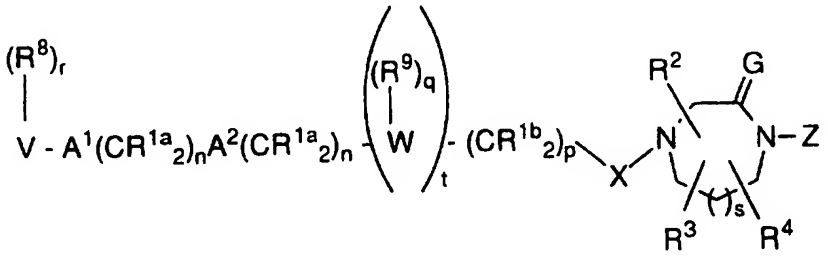
It is, therefore, an object of this invention to develop peptidomimetic compounds that do not have a thiol moiety, and that will inhibit farnesyl-protein transferase and thus, the post-translational farnesylation of proteins. It is a further object of this invention to

develop chemotherapeutic compositions containing the compounds of this invention and methods for producing the compounds of this invention.

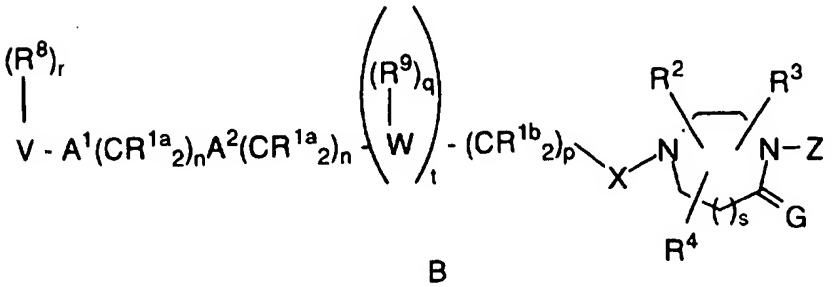
SUMMARY OF THE INVENTION

The present invention comprises peptidomimetic piperazine- or piperazinone-containing compounds which inhibit the farnesyl-protein transferase. The instant compounds lack a thiol moiety and thus offer unique advantages in terms of improved pharmacokinetic behavior in animals, prevention of thiol-dependent chemical reactions, such as rapid autoxidation and disulfide formation with endogenous thiols, and reduced systemic toxicity. Further contained in this invention are chemotherapeutic compositions containing these farnesyl transferase inhibitors and methods for their production.

The compounds of this invention are illustrated by the formulae A and B:



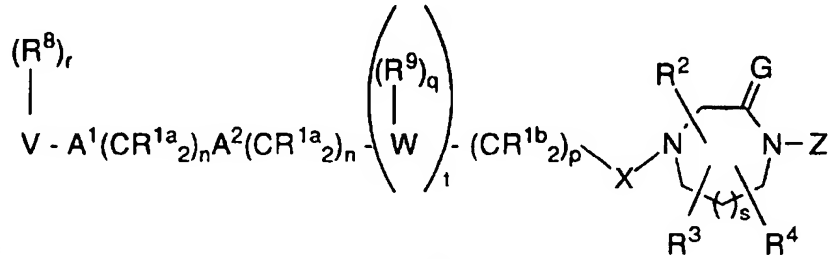
A



B

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. In a first embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula A:



A

wherein:

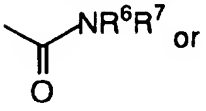
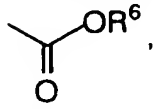
R^{1a} and R^{1b} are independently selected from:

a) hydrogen,

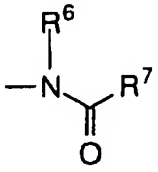
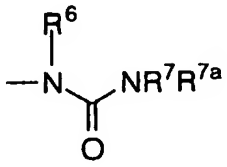
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $CN(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

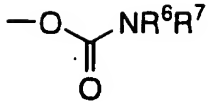
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

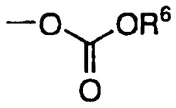
R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl,

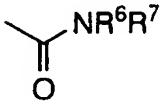
unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl,  or  , unsubstituted or substituted heterocycle,

wherein the substituted group is substituted with one or more of:

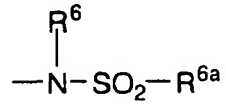
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
   e) CN,
   f) aryl or heteroaryl,
   g) perfluoro-C_{1-4} alkyl,
   h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},
5) $-NR^6R^7$,
6)  ,
7)  ,

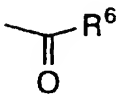
8) 

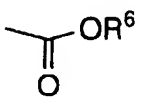
9) 

10) 

11) $-SO_2-NR^6R^7$

12) 

13) 

14) 

15) N_3,

16) F, or

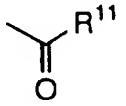
17) perfluoro-C_{1-4}-alkyl; or

R^2 and R^3 are attached to the same C atom and are combined to form -$(CH_2)_u$- wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -$N(COR^{10})$- ;

R^4 is selected from H and CH_3;

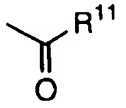
and any two of R^2, R^3 and R^4 are optionally attached to the same carbon atom;

R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring;
R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$;

R^8 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)m$-,

$R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

G is H_2 or O;

V is selected from:

a) hydrogen,

b) heterocycle,

c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is S(O)m and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)m;

W is a heterocycle;

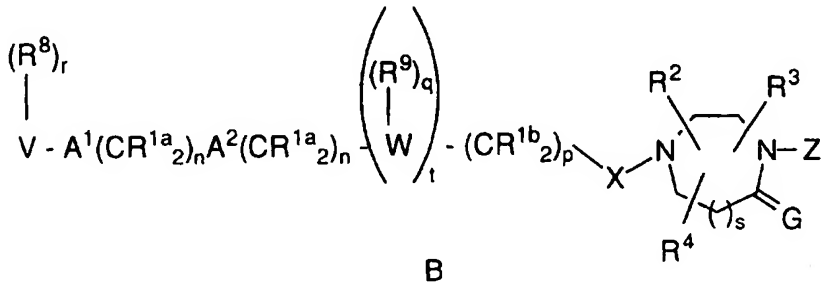
X is $-CH_2-$, -C(=O)-, or -S(=O)m-;

Z is unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:
a) C_{1-4} alkoxy,
b) NR^6R^7,
c) C_{3-6} cycloalkyl,
d) $-NR^6C(O)R^7$,
e) HO,
f) $-S(O)_mR^{6a}$,
g) halogen, or
h) perfluoroalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 1 or 2;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 0 or 1;
t is 0 or 1; and
u is 4 or 5;

or the pharmaceutically acceptable salts thereof.

In a second embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula B:



B

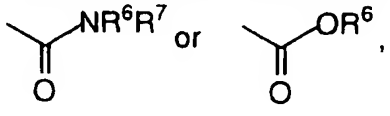
wherein:

R^{1a} and R^{1b} are independently selected from:

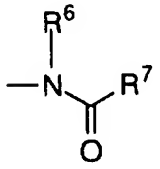
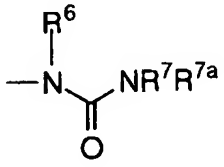
a) hydrogen,

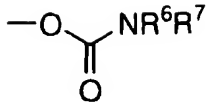
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

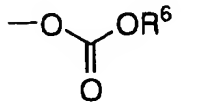
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

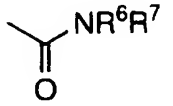
R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle,  or ,

wherein the substituted group is substituted with one or more of:

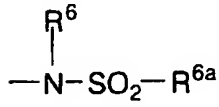
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
   e) CN,
   f) aryl or heteroaryl,
   g) perfluoro-C_{1-4} alkyl,
   h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},
5) $-NR^6R^7$,
6)  ,
7)  ,

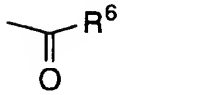
8)  ,

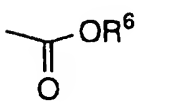
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  ,

14)  ,

15) N_3,

16) F, or

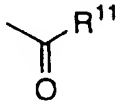
17) perfluoro-C_{1-4}-alkyl; or

R^2 and R^3 are attached to the same C atom and are combined to form -$(CH_2)_u$- wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -$N(COR^{10})$- ;

R^4 is selected from H and CH_3;

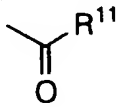
and any two of R^2, R^3 and R^4 are optionally attached to the same carbon atom;

R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring;
R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$;

R^8 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)m$-,

$R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

G is O;

V is selected from:

a) hydrogen,

b) heterocycle,

c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is S(O)m and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)m;

W is a heterocycle;

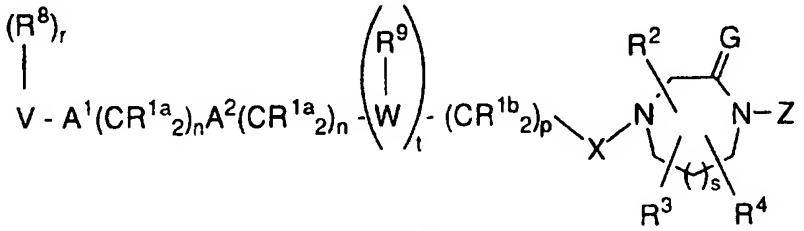
X is $-CH_2-$, -C(=O)-, or -S(=O)m-;

Z is unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:
a) C_{1-4} alkoxy,
b) NR^6R^7,
c) C_{3-6} cycloalkyl,
d) $-NR^6C(O)R^7$,
e) HO,
f) $-S(O)_mR^{6a}$,
g) halogen, or
h) perfluoroalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 1 or 2;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 1;
t is 0 or 1; and
u is 4 or 5;

or the pharmaceutically acceptable salts thereof.

In a preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula A:



A

wherein:

R^{1a} is independently selected from: hydrogen or C_1-C_6 alkyl;

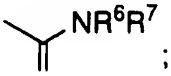
R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or C_2-C_6 alkenyl,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$- and -$N(R^{10})_2$;

R^3 and R^4 are independently selected from H and CH_3;

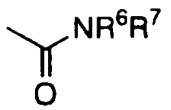
R^2 is H;  or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,

2) heterocycle,

3) OR^6,

4) SR^{6a}, SO_2R^{6a}, or

5)  ;

and any two of R^2, R^3, R^4, and R^5 are optionally attached to the same carbon atom;

R^6, R^7 and R^{7a} are independently selected from:
H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:
a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^{6a} is selected from:
C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:
a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^8 is independently selected from:
a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^9 is selected from:
a) hydrogen,
b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl. $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2,

$(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -$N(R^{10})$-, or S(O)m;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

G is H_2 or O;

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

X is $-CH_2-$ or $-C(=O)-$;

Z is unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:

a) C_{1-4} alkoxy,
b) NR^6R^7,
c) C_{3-6} cycloalkyl,
d) $-NR^6C(O)R^7$,
e) HO,
f) $-S(O)_mR^{6a}$,
g) halogen, or
h) perfluoroalkyl;

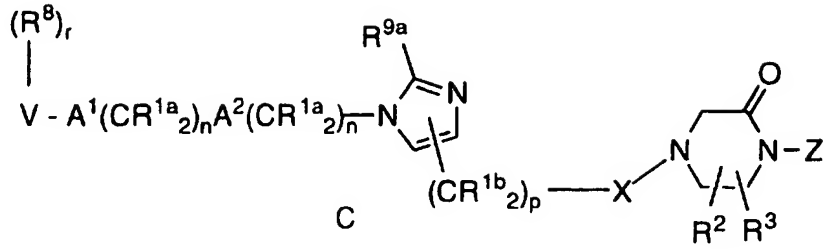
m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 0 or 1;
t is 0 or 1; and
u is 4 or 5;

provided that when G is H_2 and W is imidazolyl, then the substitutent $(R^8)_r$- V - $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ - is not H and

provided that when X is $-C(=O)-$, or $-S(=O)_m-$, then t is 1 and the substitutent $(R^8)_r$- V - $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ - is not H;

or the pharmaceutically acceptable salts thereof.

A preferred embodiment of the compounds of this invention are illustrated by the formula C:



wherein:

R^{1a} is selected from: hydrogen or C_1-C_6 alkyl;

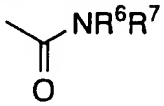
R^{1b} is independently selected from:

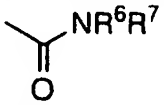
a) hydrogen,

b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from H and CH_3;

R^2 is selected from H;  or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^6,
4) SR^{6a}, SO_2R^{7a}, or
5) 

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) halogen, or
c) aryl or heterocycle;

R^{6a} is selected from:
C_{1-4} alkyl or C_{3-6} cycloalkyl,
unsubstituted or substituted with:
a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^8 is independently selected from:
a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, O, -$N(R^{10})$-, or S(O)m;

V is selected from:
a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

X is $-CH_2-$ or $-C(=O)-$;

Z is unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:

a) C_{1-4} alkoxy,

b) NR^6R^7,

c) C_{3-6} cycloalkyl,

d) $-NR^6C(O)R^7$,

e) HO,

f) $-S(O)_mR^{6a}$,

g) halogen, or

h) perfluoroalkyl;

m is 0, 1 or 2;

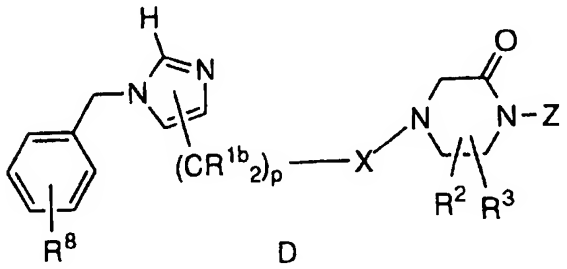
n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4; and

r is 0 to 5, provided that r is 0 when V is hydrogen;

or the pharmaceutically acceptable salts thereof.

In a more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula D:



D

wherein:

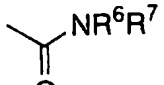
R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from H and CH_3;

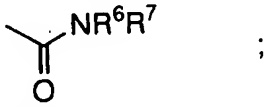
R^2 is selected from H;  or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,

2) heterocycle,

3) OR^6,

4) SR^{6a}, SO_2R^{7a}, or

5)  ;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) halogen, or

c) aryl or heterocycle;

R^{6a} is selected from:

C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) halogen, or

c) aryl or heterocycle;

R^8 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

X is -CH_2- or -C(=O)-;

Z is unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and

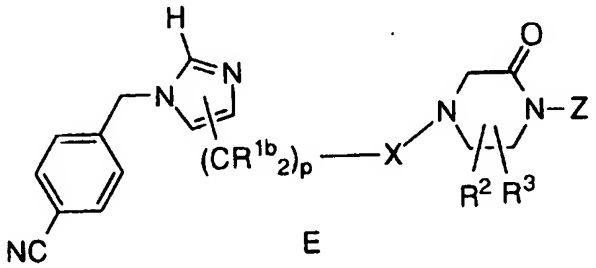
substituted C3-C6 cycloalkyl is substituted with one or two of the following:

a) C1-4 alkoxy,
b) NR^6R^7,
c) C3-6 cycloalkyl,
d) $-NR^6C(O)R^7$,
e) HO,
f) $-S(O)_mR^{6a}$,
g) halogen, or
h) perfluoroalkyl;

m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4;

or the pharmaceutically acceptable salts thereof.

In a second more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula E:



E

wherein:

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, cycloalkyl, $R^{10}O-$, $-N(R^{10})_2$ or C2-C6 alkenyl.

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^2 and R^3 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

X is -CH_2- or -C(=O)-;

Z is unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:

a) C_{1-4} alkoxy,
b) NR^6R^7,
c) C_{3-6} cycloalkyl,
d) -$NR^6C(O)R^7$,
e) HO,
f) -$S(O)_mR^{6a}$,
g) halogen, or
h) perfluoroalkyl;

m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4;

or the pharmaceutically acceptable salts thereof.

The preferred compounds of this invention are as follows:

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-4-(2,2,2-trifluoroethyl)piperazin-5-one dihydrochloride

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-4-[1-(3,3,3-trifluoropropyl)]-piperazin-5-one dihydrochloride

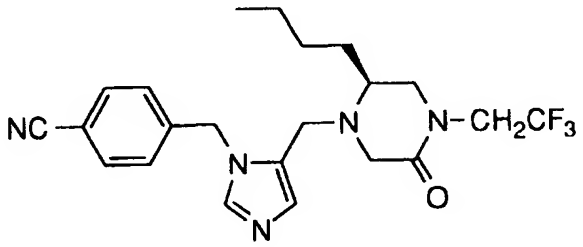
2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-4-(cyclopropylmethyl)piperazin-5-one dihydrochloride and

2(S)-*n*-Butyl-1-[3-(4-cyanobenzyl)pyridin-4-yl]-4-(2,2,2-trifluoroethyl)piperazin-5-one dihydrochloride

or the pharmaceutically acceptable salts thereof.

Specific examples of the compounds of the invention are:

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-4-(2,2,2-trifluoroethyl)piperazin-5-one dihydrochloride



or the pharmaceutically acceptable salts thereof.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. When any variable (e.g. aryl, heterocycle, R^1, R^2 etc.) occurs more than one time in any constituent, its definition on each occurence is independent at every other occurence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl.

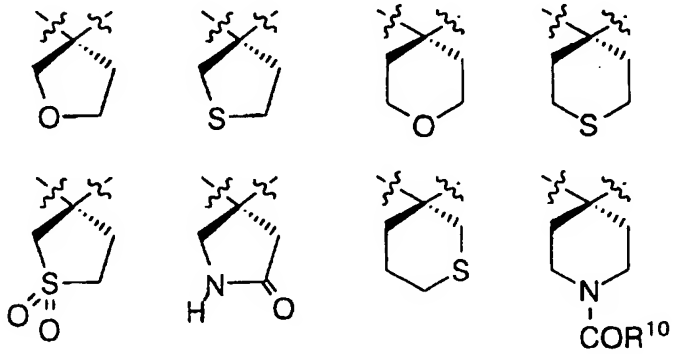
As used herein, "heteroaryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples of such heterocyclic elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, and thienyl.

As used herein in the definition of R^2 and R^3, the term "the substituted group" intended to mean a substituted C_{1-8} alkyl, substituted C_{2-8} alkenyl, substituted C_{2-8} alkynyl, substituted aryl or substituted heterocycle from which the substitutent(s) R^2 and R^3 are selected.

As used herein in the definition of R^6, R^{6a}, R^7 and R^{7a}, the substituted C_{1-8} alkyl, substituted C_{3-6} cycloalkyl, substituted aroyl, substituted aryl, substituted heteroaroyl, substituted arylsulfonyl, substituted heteroarylsulfonyl and substituted heterocycle include moieties containing from 1 to 3 substitutents in addition to the point of attachment to the rest of the compound.

When R^2 and R^3 are combined to form - $(CH_2)_u$ -, cyclic moieties are formed. Examples of such cyclic moieties include, but are not limited to:

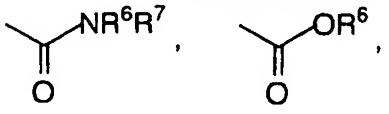
In addition, such cyclic moieties may optionally include a heteroatom(s). Examples of such heteroatom-containing cyclic moieties include, but are not limited to:



Lines drawn into the ring systems from substituents (such as from R^2, R^3, R^4 etc.) indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Preferably, R^{1a} and R^{1b} are independently selected from: hydrogen, $-N(R^{10})_2$, $R^{10}C(O)NR^{10}-$ or unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted phenyl, $-N(R^{10})_2$, $R^{10}O-$ and $R^{10}C(O)NR^{10}-$.

Preferably, R^2 is selected from: H,



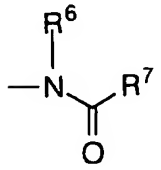
and an unsubstituted or substituted group, the group selected from C_{1-8} alkyl, C_{2-8} alkenyl and C_{2-8} alkynyl;

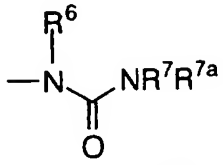
wherein the substituted group is substituted with one or more of:

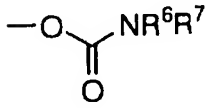
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
2) C_{3-6} cycloalkyl,
3) OR^6,

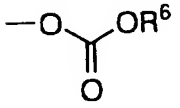
4) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},

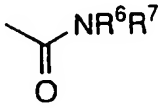
5) $-NR^6R^7$,

6)  ,

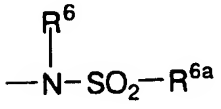
7)  ,

8)  ,

9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

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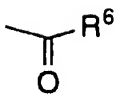
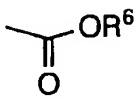
13)  ,

14)  ,

15) N_3, or

16) F.

Preferably, R^3 is selected from: hydrogen and C_1-C_6 alkyl.

Preferably, R^4 and R^5 are hydrogen.

Preferably, R^6, R^7 and R^{7a} is selected from: hydrogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted aryl and unsubstituted or substituted cycloalkyl.

Preferably, R^{6a} is unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted aryl and unsubstituted or substituted cycloalkyl.

Preferably, R^9 is hydrogen or methyl. Most preferably, R^a is hydrogen.

Preferably, R^{10} is selected from H, C_1-C_6 alkyl and benzyl.

Preferably, A^1 and A^2 are independently selected from: a bond, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)2N(R^{10})- and-N(R^{10})S(O)2-.

Preferably, V is selected from hydrogen, heterocycle and aryl. More preferably, V is phenyl.

Preferably, Z is unsubstituted or substituted C_1-C_6 alkyl.

Preferably, W is selected from imidazolinyl, imidazolyl, oxazolyl, pyrazolyl, pyyrolidinyl, thiazolyl and pyridyl. More preferably, W is selected from imidazolyl and pyridyl.

Preferably, n and r are independently 0, 1, or 2.

Preferably p is 1, 2 or 3.

Preferably s is 0.

Preferably t is 1.

It is intended that the definition of any substituent or variable (e.g., R^{1a}, R^9, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, $-N(R^{10})_2$ represents -NHH, $-NHCH_3$, $-NHC_2H_5$, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the Schemes 1-21, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R, R^a and R^b, as shown in the Schemes, represent the substituents R^2, R^3, R^4, and R^5;

however their point of attachment to the ring is illustrative only and is not meant to be limiting. Substituent Z', as shown in the Schemes, represents an alkyl moiety or a substitutent on an alkyl moiety such that $Z'CH_2$- is the substiutent Z as defined hereinabove.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes.

Synopsis of Schemes 1-21:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. In Scheme 1, for example, the synthesis of 2-alkyl substituted piperazines is outlined, and is essentially that described by J. S. Kiely and S. R. Priebe in Organic Preparations and Proceedings Int., **1990**, *22*, 761-768. Boc-protected amino acids I, available commercially or by procedures known to those skilled in the art, can be coupled to N-benzyl amino acid esters using a variety of dehydrating agents such as DCC (dicyclohexycarbodiimide) or EDC·HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) in a solvent such as methylene chloride , chloroform, dichloroethane, or in dimethylformamide. The product II is then deprotected with acid, for example hydrogen chloride in chloroform or ethyl acetate, or trifluoroacetic acid in methylene chloride, and cyclized under weakly basic conditions to give the diketopiperazine III. Reduction of III with lithium aluminum hydride in refluxing ether gives the piperazine IV, which is protected as the Boc derivative V. The N-benzyl group can be cleaved under standard conditions of hydrogenation, e.g., 10% palladium on carbon at 60 psi hydrogen on a Parr apparatus for 24-48 h. The product VI can be reductively alkylated with a suitably substituted aldehyde to provide the protected piperazine VII; a final acid deprotection as previously described gives the intermediate VIII (Scheme 2). The intermediate VIII can itself be reductively alkylated with a variety of aldehydes, such as IX. The aldehydes can be prepared

by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**, *67*, 69-75, from the appropriate amino acid (Scheme 3). The reductive alkylation can be accomplished at pH 5-7 with a variety of reducing agents, such as sodium triacetoxyborohydride or sodium cyanoborohydride in a solvent such as dichloroethane, methanol or dimethylformamide. The product X can be deprotected to give the final compounds XI with trifluoroacetic acid in methylene chloride. The final product XI is isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine XI can further be selectively protected to obtain XII, which can subsequently be reductively alkylated with a second aldehyde to obtain XIII. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole XV can be accomplished by literature procedures.

Alternatively, the piperazine intermediate VIII can be reductively alkylated with other aldehydes such as 1-trityl-4-imidazolyl-carboxaldehyde or 1-trityl-4-imidazolylacetaldehyde, to give products such as XVI (Scheme 4). The trityl protecting group can be removed from XVI to give XVII, or alternatively, XVI can first be treated with an alkyl halide then subsequently deprotected to give the alkylated imidazole XVIII. Alternatively, the intermediate VIII can be acylated or sulfonylated by standard techniques. The imidazole acetic acid XIX can be converted to the acetate XXI by standard procedures, and XXI can be first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester XXII. Hydrolysis and reaction with piperazine VIII in the presence of condensing reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) leads to acylated products such as XXIV.

If the piperazine VIII is reductively alkylated with an aldehyde which also has a protected hydroxyl group, such as XXV in Scheme 6, the protecting groups can be subsequently removed to unmask the hydroxyl group (Schemes 6, 7). The alcohol can be oxidized under standard conditions to *e.g.* an aldehyde, which can then

be reacted with a variety of organometallic reagents such as Grignard reagents, to obtain secondary alcohols such as XXIX. In addition, the fully deprotected amino alcohol XXX can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as XXXI (Scheme 7), or tertiary amines.

The Boc protected amino alcohol XXVII can also be utilized to synthesize 2-aziridinylmethylpiperazines such as XXXII (Scheme 8). Treating XXVII with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of aziridine XXXII. The aziridine reacted in the presence of a nucleophile, such as a thiol, in the presence of base to yield the protected ring-opened product XXXIII.

In addition, the piperazine VIII can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as XXXIX. When R' is an aryl group, XXXIX can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce XL. Alternatively, the amine protecting group in XXXIX can be removed, and O-alkylated phenolic amines such as XLI produced.

Depending on the identity of the amino acid I, various side chains can be incorporated into the piperazine. For example when I is the Boc-protected β-benzyl ester of aspartic acid, the intermediate diketopiperazine XLII (where n=1 and R=benzyl) is obtained, as shown in Scheme 10. Subsequent lithium aluminum hydride reduction reduces the ester to the alcohol XLIII, which can then be reacted with a variety of alkylating agents such as an alkyl iodide, under basic conditions, for example, sodium hydride in dimethylformamide or tetrahydrofuran. The resulting ether XLIV can then be carried on to final products as described in Schemes 1-9.

N-Alkyl piperazines can be prepared as described in Scheme 11. An alkyl amine XLV is reacted with *bis* -chloroethyl amine hydrochloride (XLVI) in refluxing *n* -butanol to furnish compounds XLVII. The resulting piperazines XLVII can then be carried on to final products as described in Schemes 3-9.

Piperazin-5-ones can be prepared as shown in Scheme 12. Reductive amination of Boc-protected amino aldehydes XLIX (prepared from I as described previously) gives rise to compound L. This is then reacted with bromoacetyl bromide under Schotten-Baumann conditions; ring closure is effected with a base such as sodium hydride in a polar aprotic solvent such as dimethylformamide to give LI. The carbamate protecting group is removed under acidic conditions such as trifluoroacetic acid in methylene chloride, or hydrogen chloride gas in methanol or ethyl acetate, and the resulting piperazine can then be carried on to final products as described in Schemes 3-9.

The isomeric piperazin-3-ones can be prepared as described in Scheme 13. The imine formed from arylcarboxamides LII and 2-aminoglycinal diethyl acetal (LIII) can be reduced under a variety of conditions, including sodium triacetoxyborohydride in dichloroethane, to give the amine LIV. Amino acids I can be coupled to amines LIV under standard conditions, and the resulting amide LV when treated with aqueous acid in tetrahydrofuran can cyclize to the unsaturated LVI. Catalytic hydrogenation under standard conditions gives the requisite intermediate LVII, which is elaborated to final products as described in Schemes 3-9.

Reaction Scheme 14 provides an illustrative example the synthesis of compounds of the instant invention wherein the substituents R^2 and R^3 are combined to form - $(CH_2)_u$ -. For example, 1-aminocyclohexane-1-carboxylic acid LVIII can be converted to the spiropiperazine LXVI essentially according to the procedures outlined in Schemes 1 and 2. The piperazine intermediate LXVI can be deprotected as before, and carried on to final products as described in Schemes 3-9. It is understood that reagents utilized to provide the imidazolylalkyl substituent may be readily replaced by other reagents well known in the art and readily available to provide other N-substituents on the piperazine.

The aldehyde XLIX from Scheme 12 can also be reductively alkylated with an alkyl amine as shown in Scheme 15. The product LXVIII can be converted to a piperazinone by acylation with

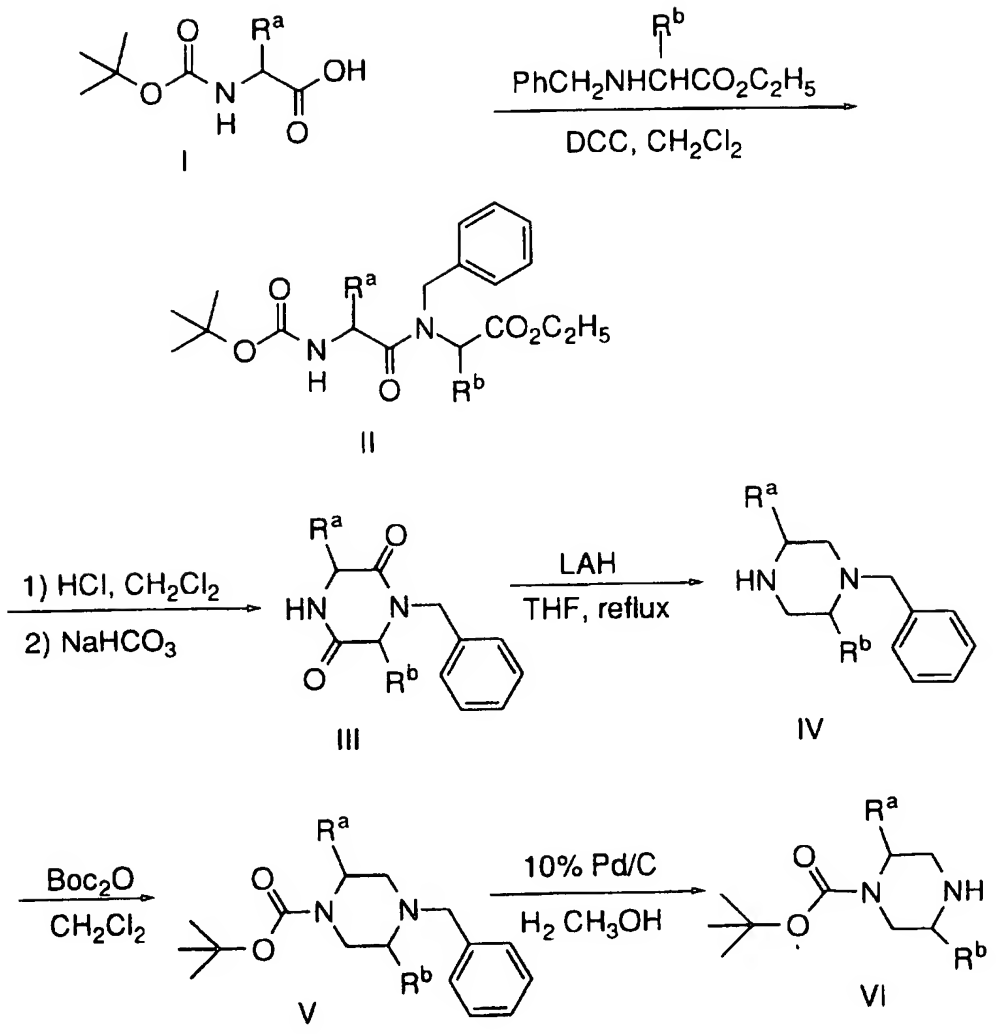
chloroacetyl chloride to give LXIX, followed by base-induced cyclization to LXX. Deprotection, followed by reductive alkylation with a protected imidazole carboxaldehyde leads to LXXII, which can be alkylation with an arylmethylhalide to give the imidazolium salt LXXIII. Final removal of protecting groups by either solvolysis with a lower alkyl alcohol, such as methanol, or treatment with triethylsilane in methylene chloride in the presence of trifluoroacetic acid gives the final product LXXIV.

Scheme 16 illustrates the use of an optionally substituted homoserine lactone LXXV to prepare a Boc-protected piperazinone LXXVIII. Intermediate LXXVIII may be deprotected and reductively alkylated or acylated as illustrated in the previous Schemes. Alternatively, the hydroxyl moiety of intermediate LXXVIII may be mesylated and displaced by a suitable nucleophile, such as the sodium salt of ethane thiol, to provide an intermediate LXXIX. Intermediate LXXVIII may also be oxidized to provide the carboxylic acid on intermediate LXXXX, which can be utilized form an ester or amide moiety.

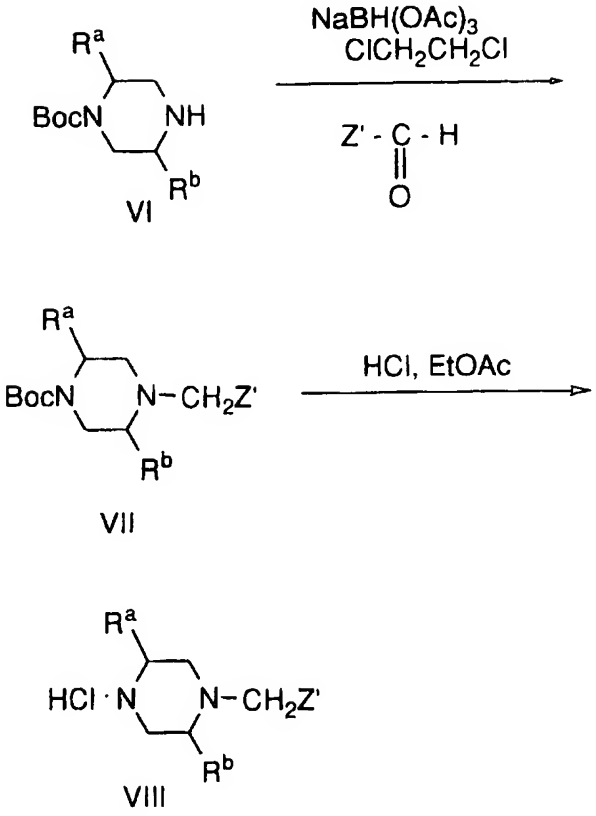
Amino acids of the general formula LXXXI which have a sidechain not found in natural amino acids may be prepared by the reactions illustrated in Scheme 17 starting with the readily prepared imine LXXXII.

Schemes 18-21 illustrate syntheses of suitably substituted aldehydes useful in the syntheses of the instant compounds wherein the variable W is present as a pyridyl moiety. Similar synthetic strategies for preparing alkanols that incorporate other heterocyclic moieties for variable W are also well known in the art.

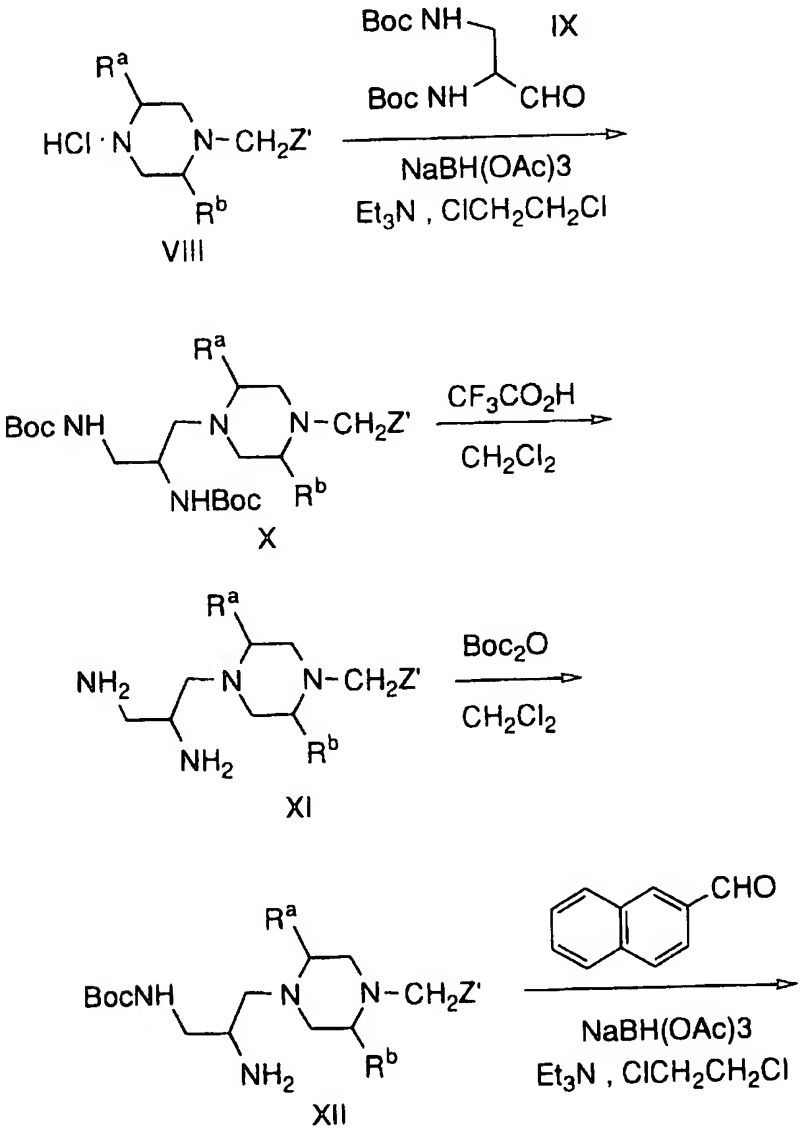
SCHEME 1


PhCH2NHCHCO2C2H5
DCC, CH2Cl2
1) HCl, CH2Cl2
2) NaHCO3
LAH
THF, reflux
Boc2O
CH2Cl2
10% Pd/C
H2 CH3OH
I
II
III
IV
V
VI

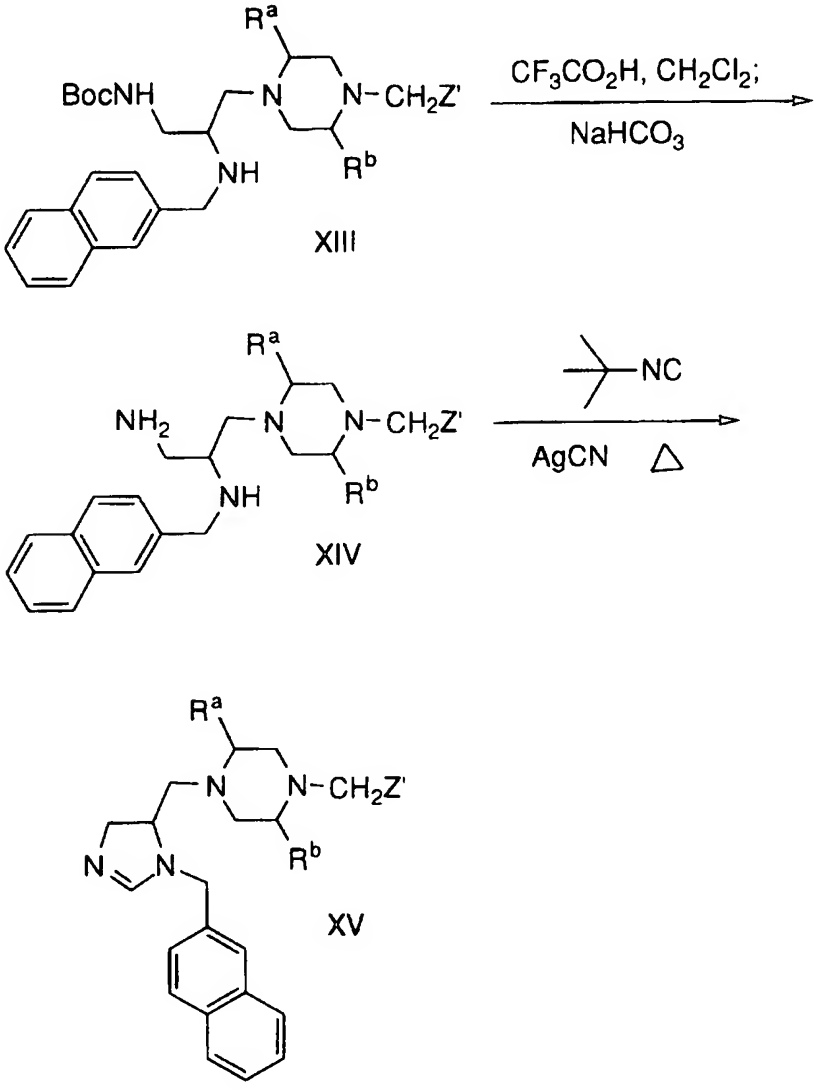
SCHEME 2


NaBH(OAc)3
ClCH2CH2Cl
Z' - C - H
O
Ra
BocN
NH
Rb
VI
HCl, EtOAc
N−CH2Z'
VII
HCl · N
VIII

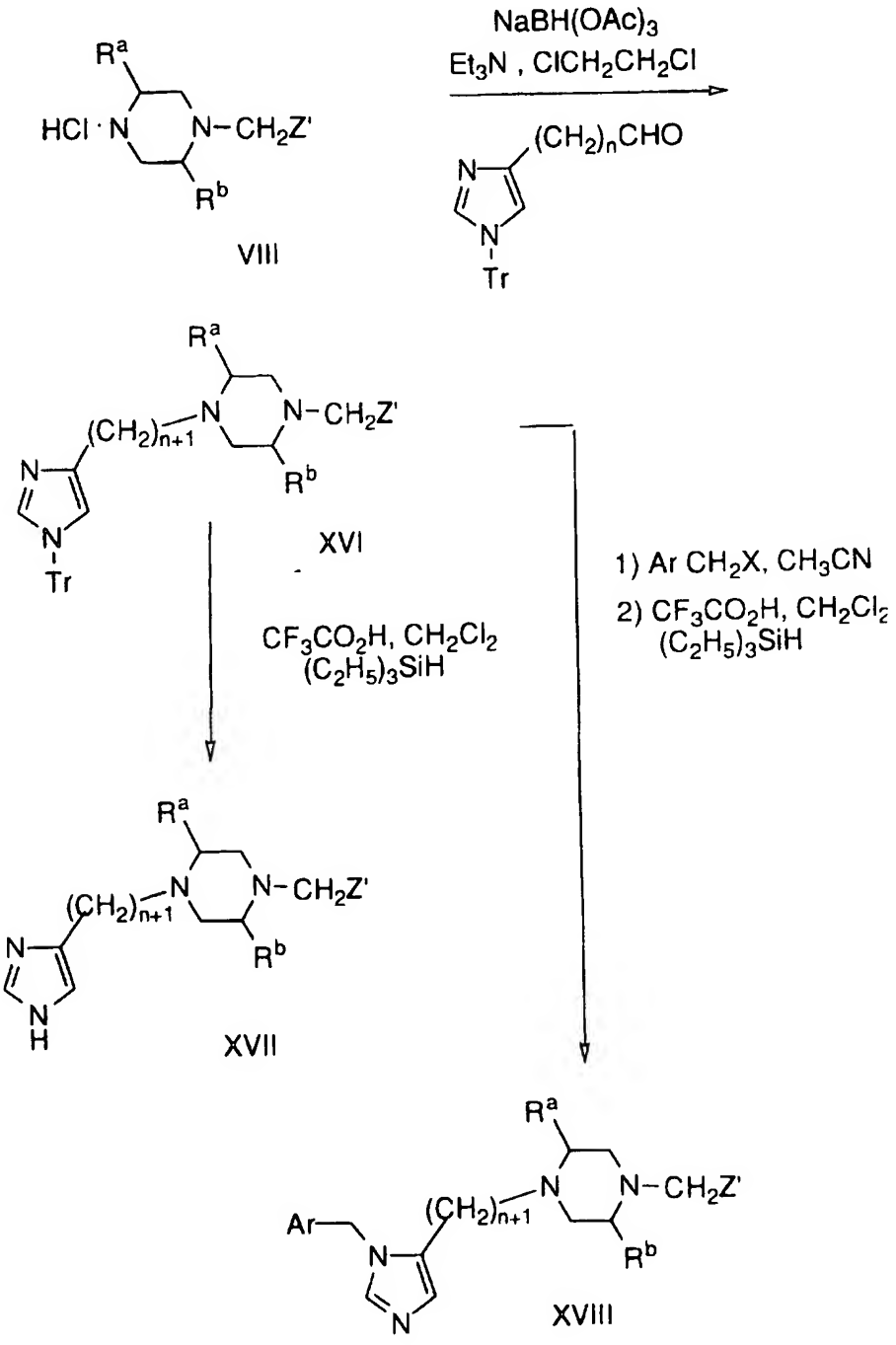
SCHEME 3


Boc NH
IX
Boc NH
CHO
R^a
HCl · N
N–CH_2Z'
R^b
VIII
NaBH(OAc)3
Et_3N , $ClCH_2CH_2Cl$
R^a
Boc NH
N
N–CH_2Z'
NHBoc
R^b
X
CF_3CO_2H
CH_2Cl_2
R^a
NH_2
N
N–CH_2Z'
NH_2
R^b
XI
Boc_2O
CH_2Cl_2
R^a
BocNH
N
N–CH_2Z'
NH_2
R^b
XII
CHO
NaBH(OAc)3
Et_3N , $ClCH_2CH_2Cl$

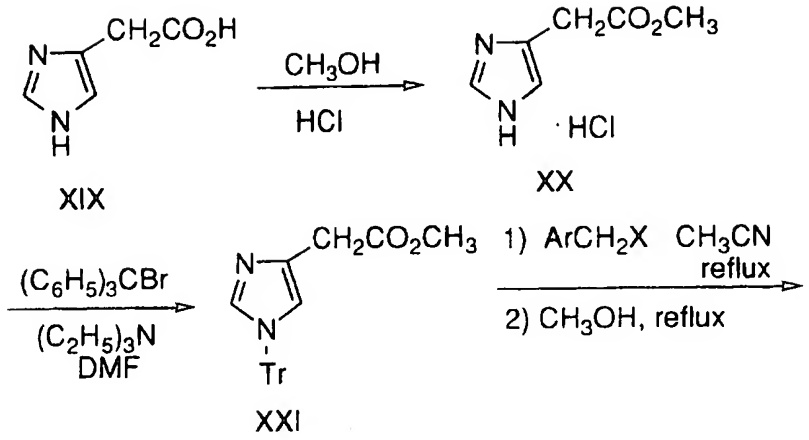
SCHEME 3 (continued)



SCHEME 4


NaBH(OAc)3
Et3N , ClCH2CH2Cl
(CH2)nCHO
Tr
VIII
XVI
1) Ar CH2X, CH3CN
2) CF3CO2H, CH2Cl2
(C2H5)3SiH
CF3CO2H, CH2Cl2
(C2H5)3SiH
XVII
XVIII

SCHEME 5



XIX

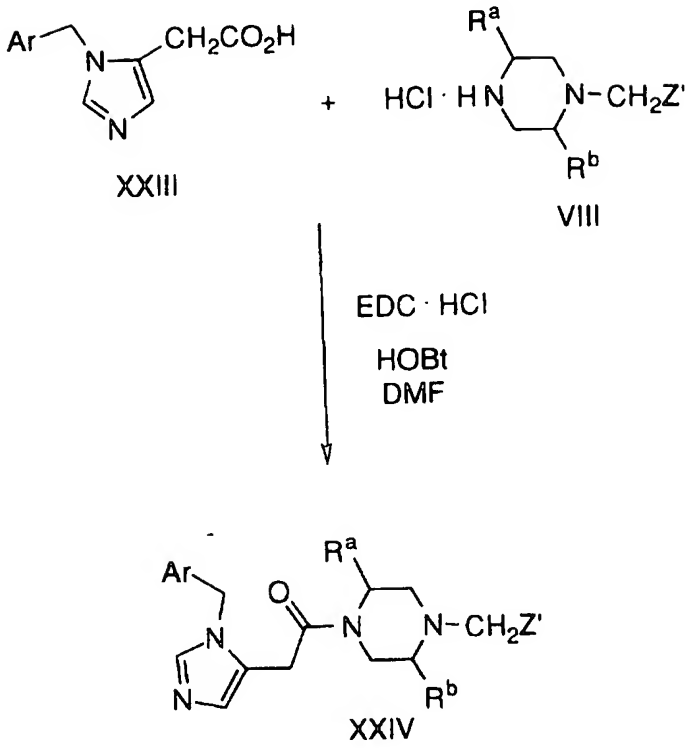
XX

XXI

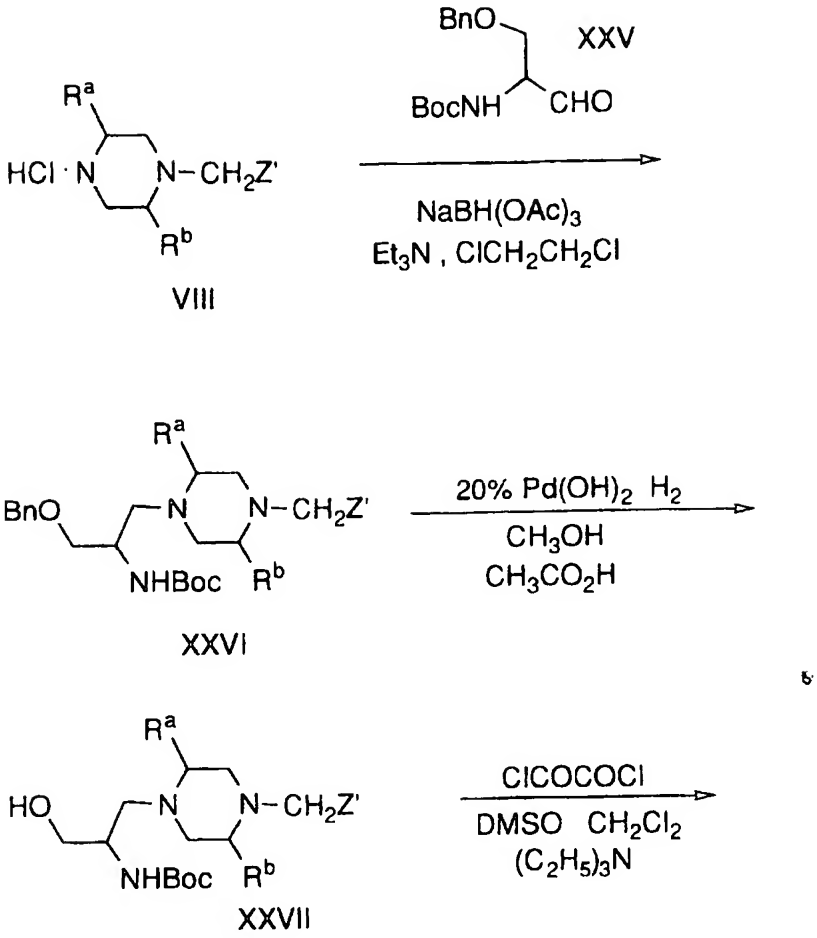
XXII

XXIII

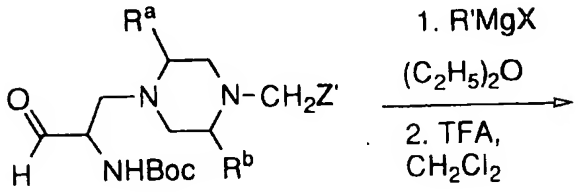
SCHEME 5 (continued)



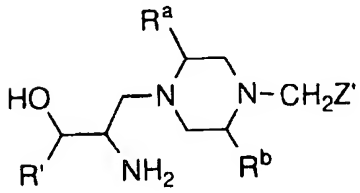
SCHEME 6


BnO
XXV
BocNH
CHO
R^a
HCl · N
N–CH_2Z'
R^b
VIII
$NaBH(OAc)_3$
Et_3N , $ClCH_2CH_2Cl$
R^a
BnO
N
N–CH_2Z'
NHBoc
R^b
XXVI
20% $Pd(OH)_2$ H_2
CH_3OH
CH_3CO_2H
R^a
HO
N
N–CH_2Z'
NHBoc
R^b
XXVII
ClCOCOCl
DMSO CH_2Cl_2
$(C_2H_5)_3N$

SCHEME 6 (CONTINUED)

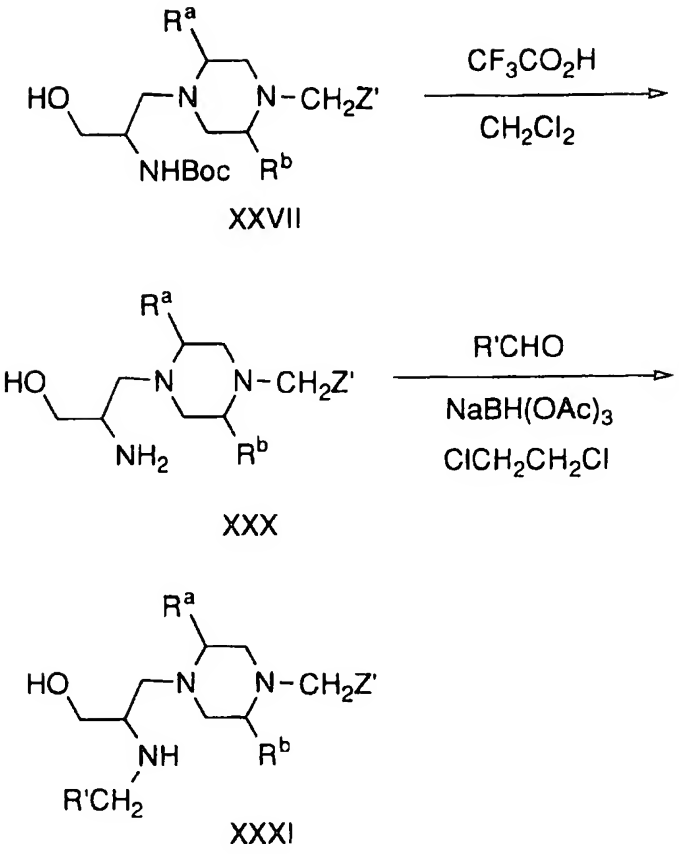


XXVIII

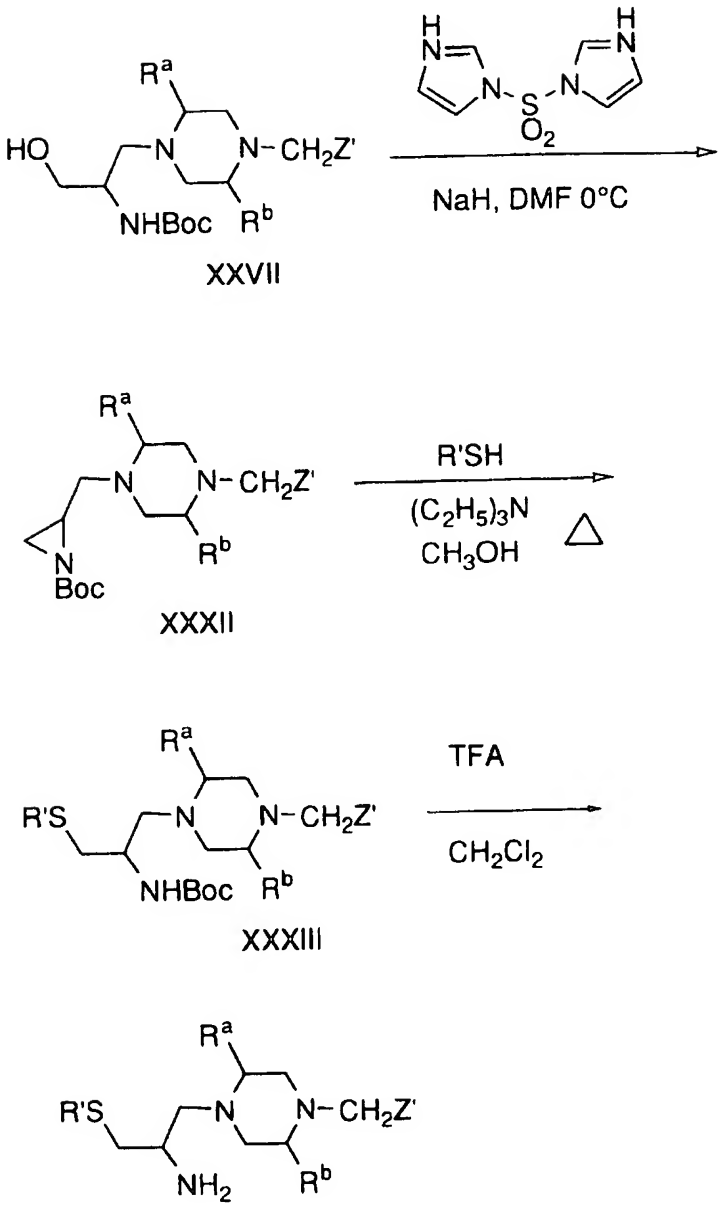


XXIX

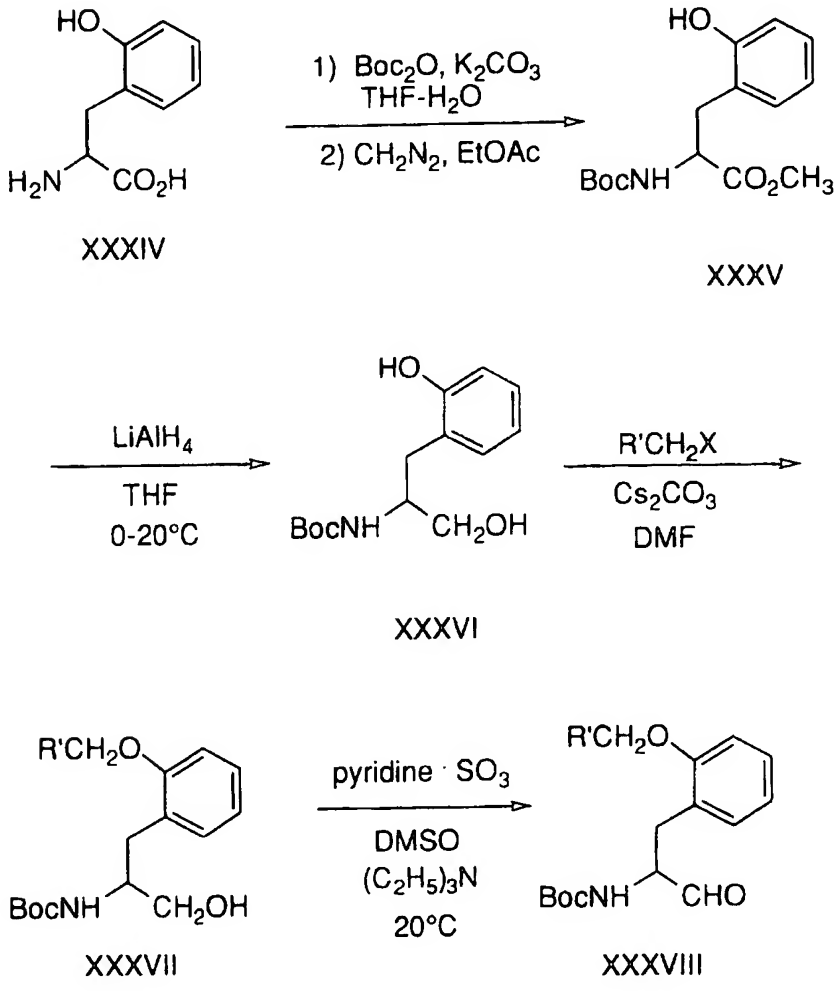
SCHEME 7


Ra
HO
N
N-CH2Z'
NHBoc
Rb
CF3CO2H
CH2Cl2
XXVII
NH2
R'CHO
NaBH(OAc)3
ClCH2CH2Cl
XXX
NH
R'CH2
XXXI

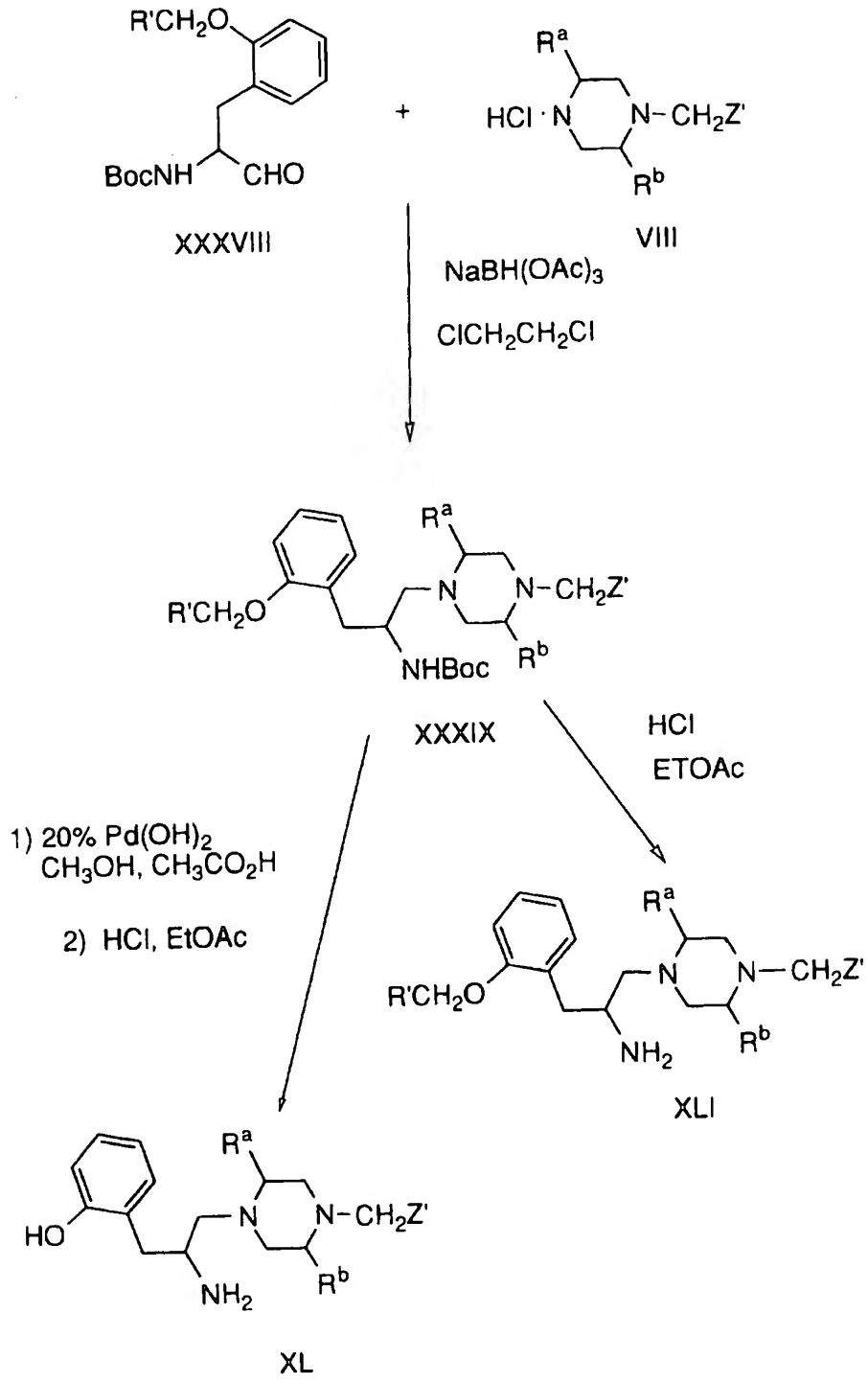
SCHEME 8


Ra
HO
N
N-CH2Z'
NHBoc
Rb
XXVII
H
N
N
S
O2
NaH, DMF 0°C
Ra
N
N-CH2Z'
Rb
N
Boc
XXXII
R'SH
(C2H5)3N
CH3OH
Ra
R'S
N
N-CH2Z'
NHBoc
Rb
XXXIII
TFA
CH2Cl2
Ra
R'S
N
N-CH2Z'
NH2
Rb

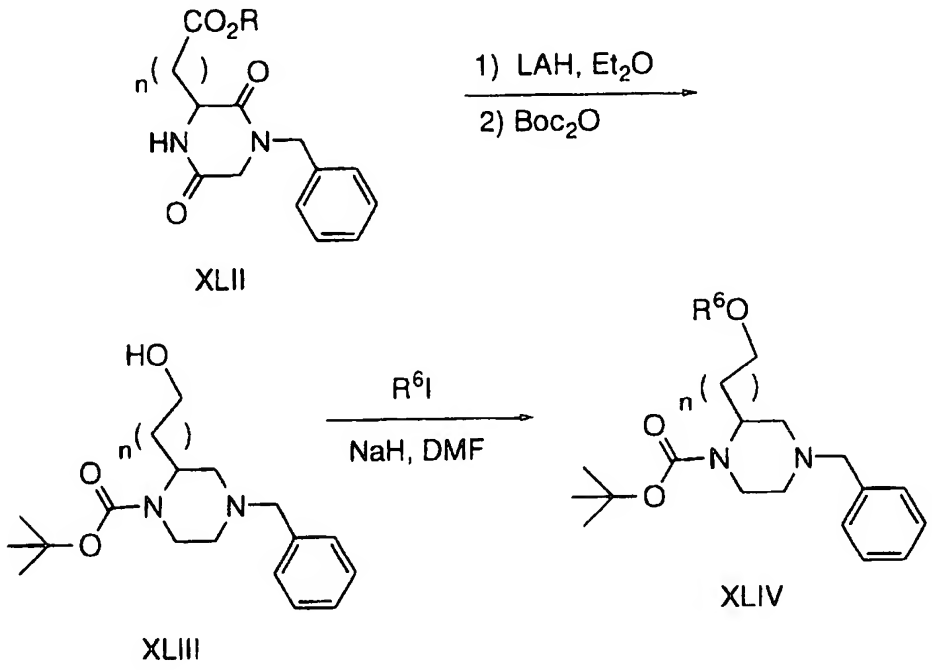
SCHEME 9


HO
H2N
CO2H
XXXIV
1) Boc2O, K2CO3
THF-H2O
2) CH2N2, EtOAc
HO
BocNH
CO2CH3
XXXV
LiAlH4
THF
0-20°C
HO
BocNH
CH2OH
XXXVI
R'CH2X
Cs2CO3
DMF
R'CH2O
BocNH
CH2OH
XXXVII
pyridine · SO3
DMSO
(C2H5)3N
20°C
R'CH2O
BocNH
CHO
XXXVIII

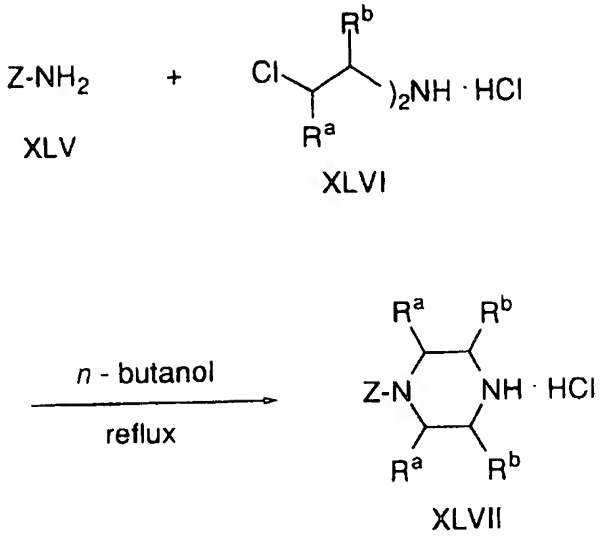
SCHEME 9 (continued)



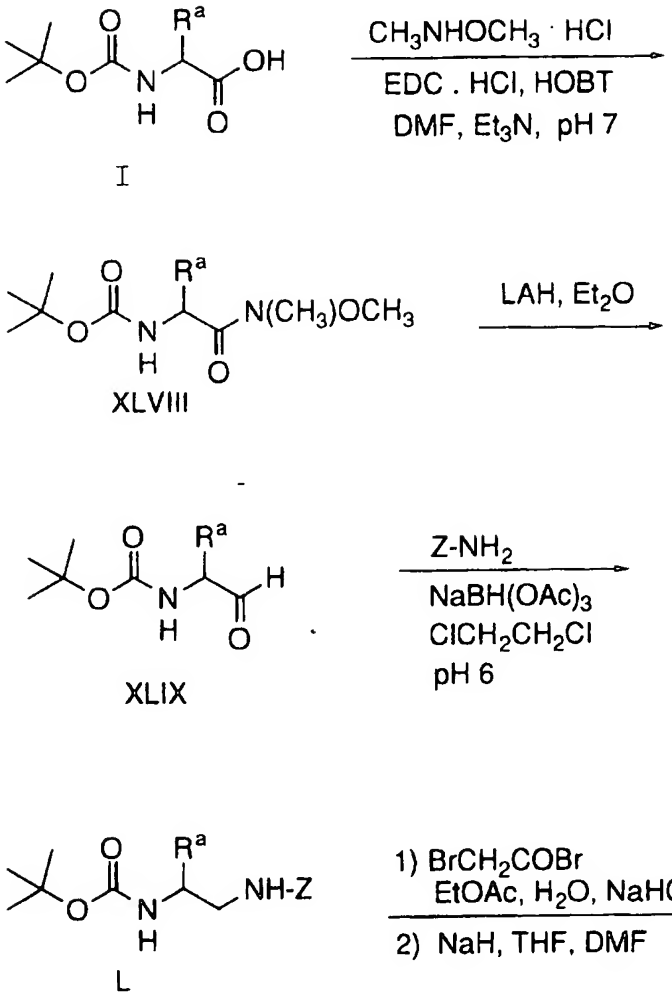
SCHEME 10


CO2R
n
O
HN
N
O
1) LAH, Et2O
2) Boc2O
XLII
HO
n
O
N
N
O
R6I
NaH, DMF
R6O
n
O
N
N
O
XLIII
XLIV

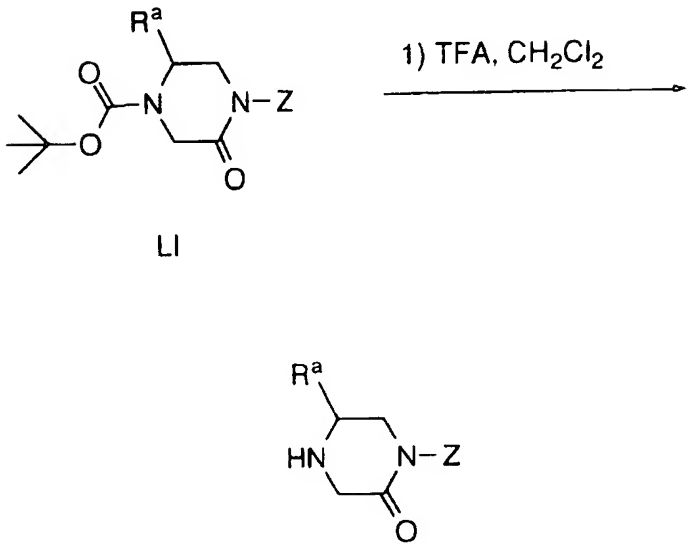
SCHEME 11


Z-NH2
+
Cl
Rb
Ra
)2NH · HCl
XLV
XLVI
n - butanol
reflux
Z-N
NH · HCl
Ra
Rb
XLVII

SCHEME 12

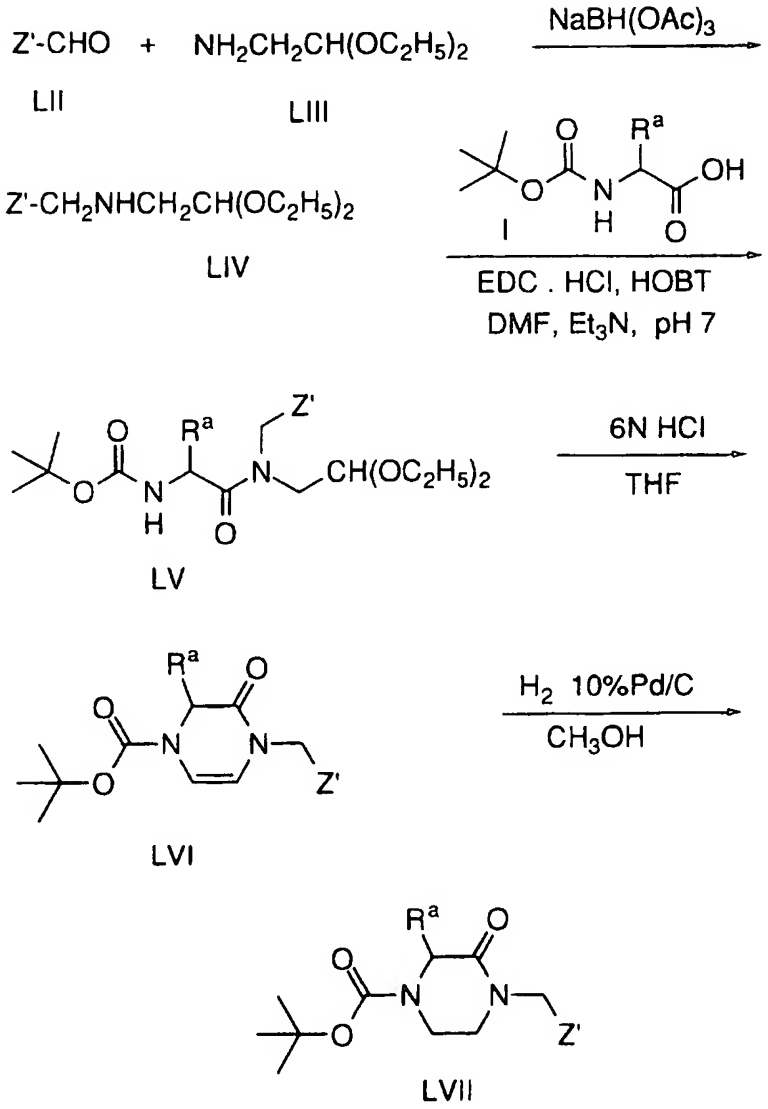

Ra
O
OH
N
H
O
CH3NHOCH3 · HCl
EDC . HCl, HOBT
DMF, Et3N, pH 7
I
Ra
N(CH3)OCH3
LAH, Et2O
XLVIII
Ra
H
Z-NH2
NaBH(OAc)3
ClCH2CH2Cl
pH 6
XLIX
Ra
NH-Z
1) BrCH2COBr
EtOAc, H2O, NaHCO3
2) NaH, THF, DMF
L

SCHEME 12 (CONT'D)

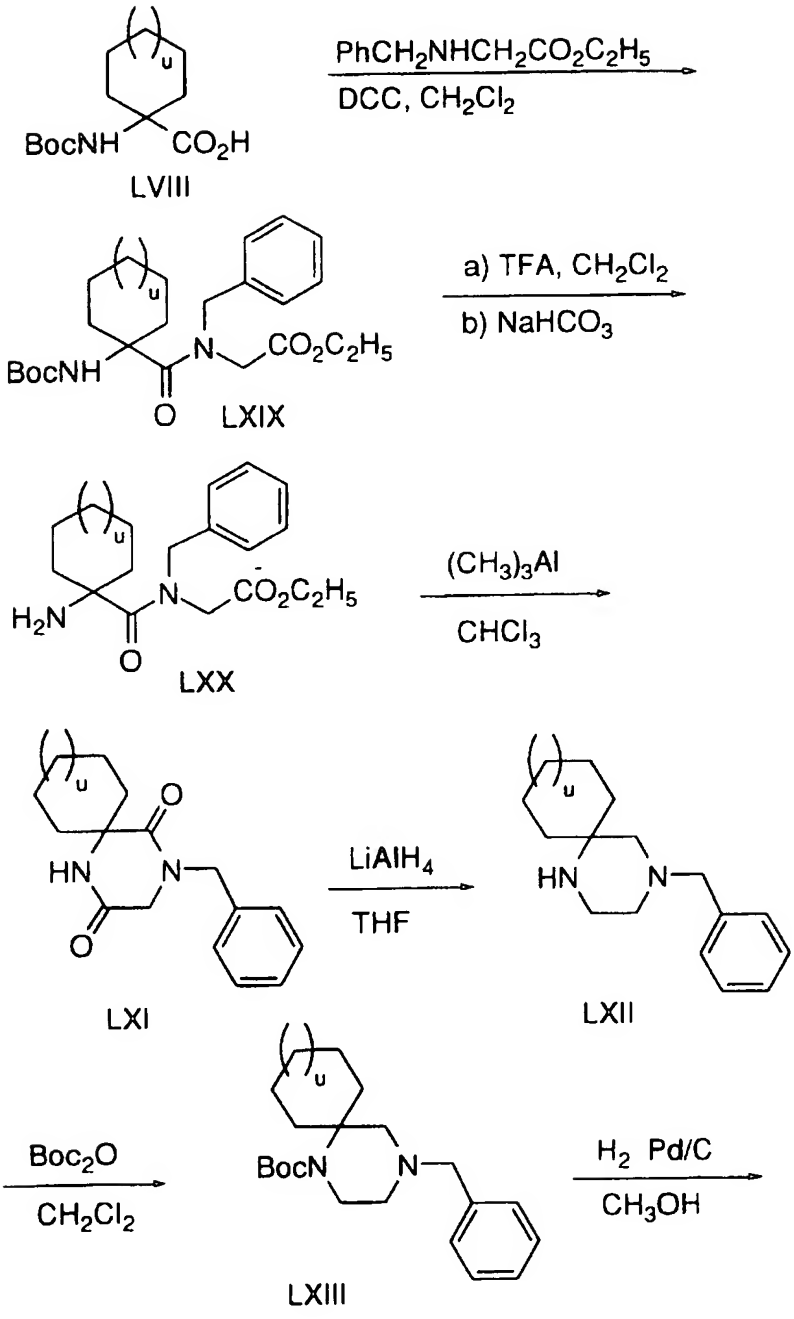


LI

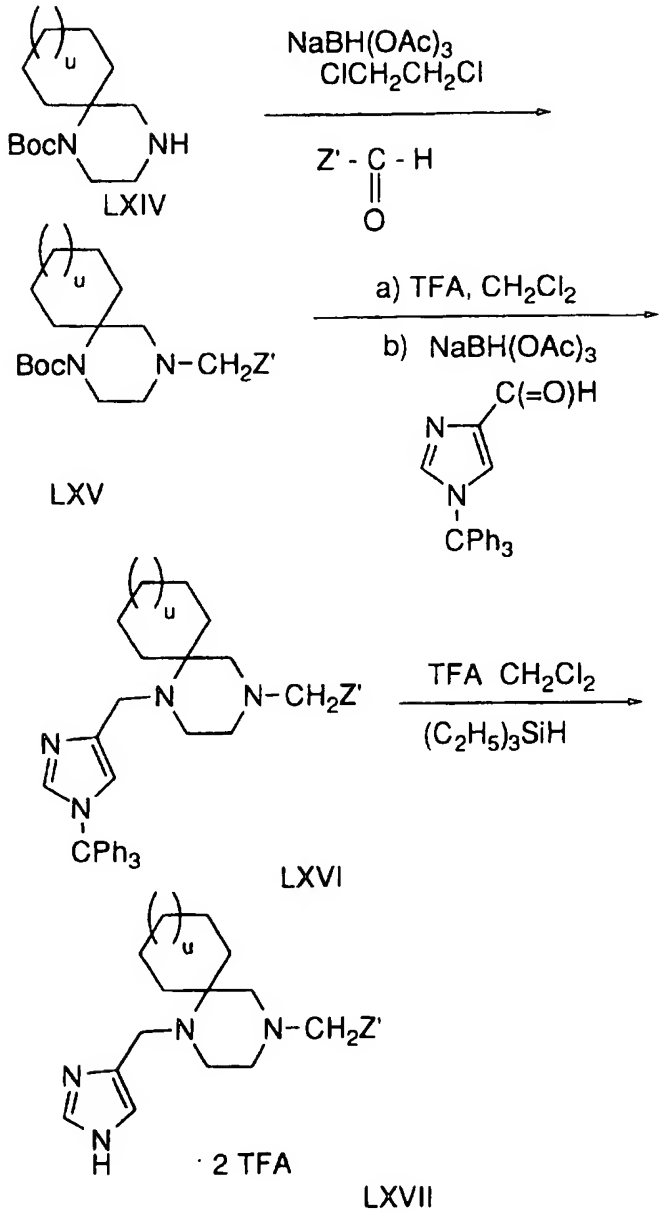
SCHEME 13


Z'-CHO + NH2CH2CH(OC2H5)2
NaBH(OAc)3
LII
LIII
Z'-CH2NHCH2CH(OC2H5)2
LIV
I
EDC . HCl, HOBT
DMF, Et3N, pH 7
6N HCl
THF
LV
H2 10%Pd/C
CH3OH
LVI
LVII

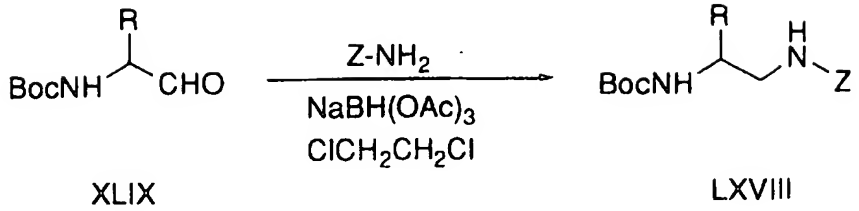
SCHEME 14


PhCH2NHCH2CO2C2H5
DCC, CH2Cl2
BocNH
CO2H
LVIII
a) TFA, CH2Cl2
b) NaHCO3
BocNH
N
CO2C2H5
O
LXIX
H2N
N
CO2C2H5
O
LXX
(CH3)3Al
CHCl3
HN
N
O
O
LXI
LiAlH4
THF
HN
N
LXII
Boc2O
CH2Cl2
BocN
N
LXIII
H2 Pd/C
CH3OH

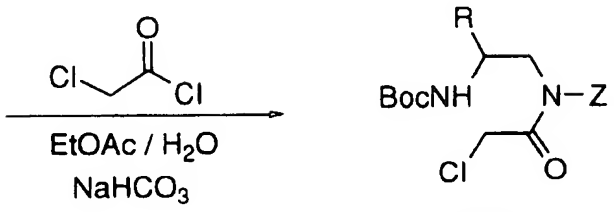
SCHEME 14 (continued)



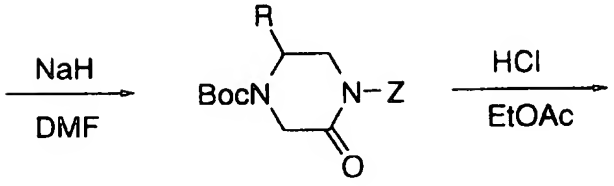
SCHEME 15



XLIX LXVIII

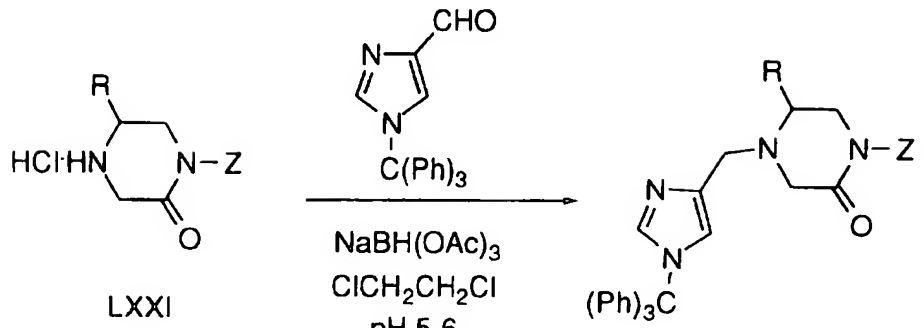


LXIX



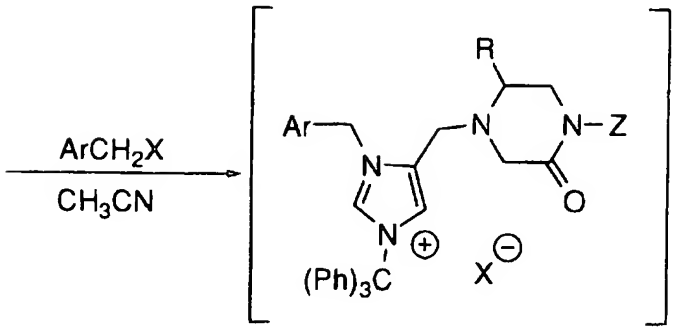
LXX

SCHEME 15 (continued)

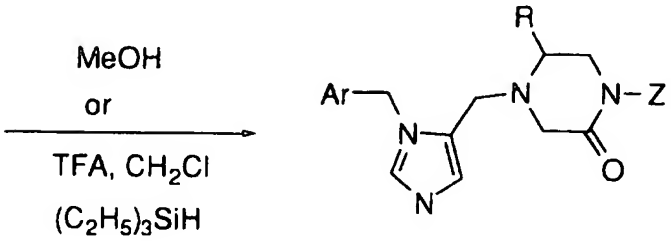


LXXI

LXXII

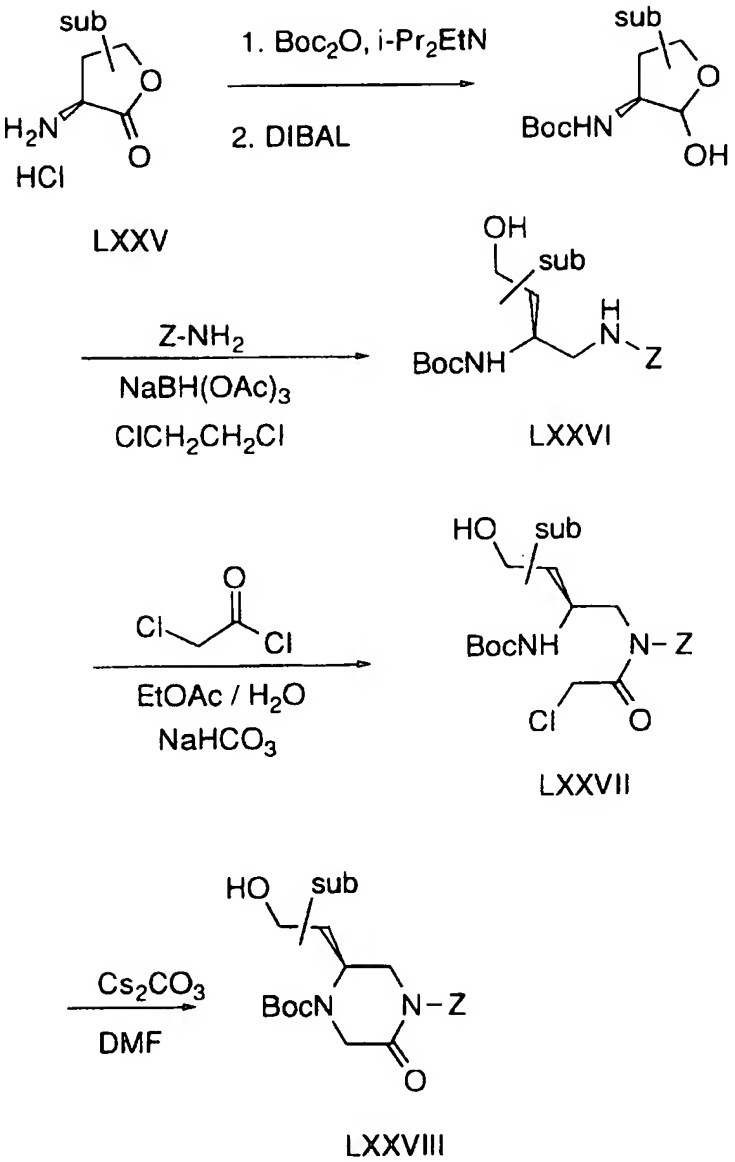


LXXIII

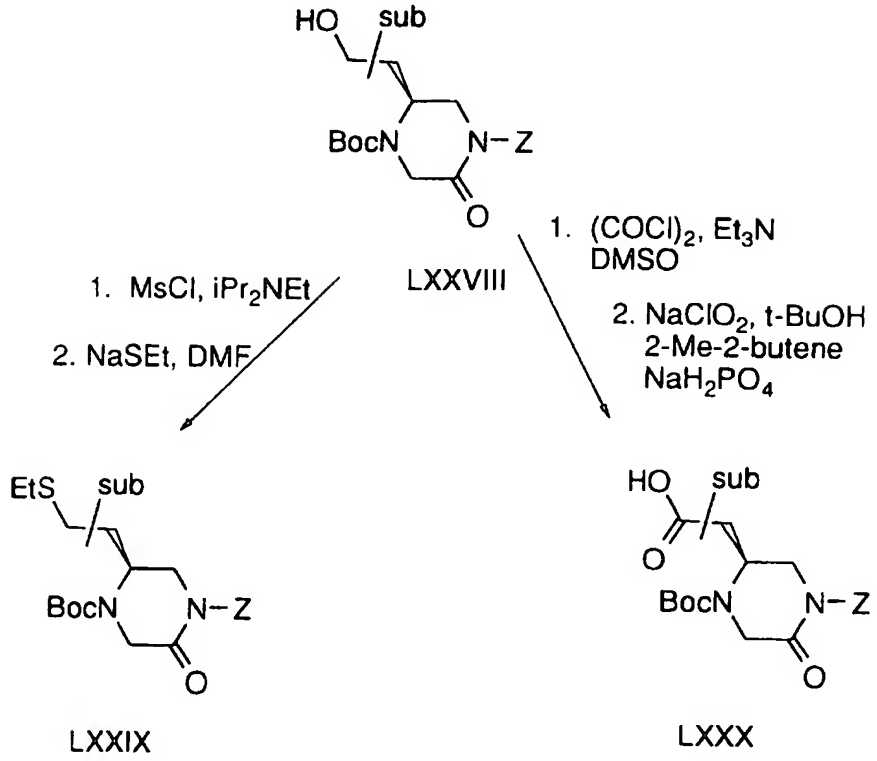


LXXIV

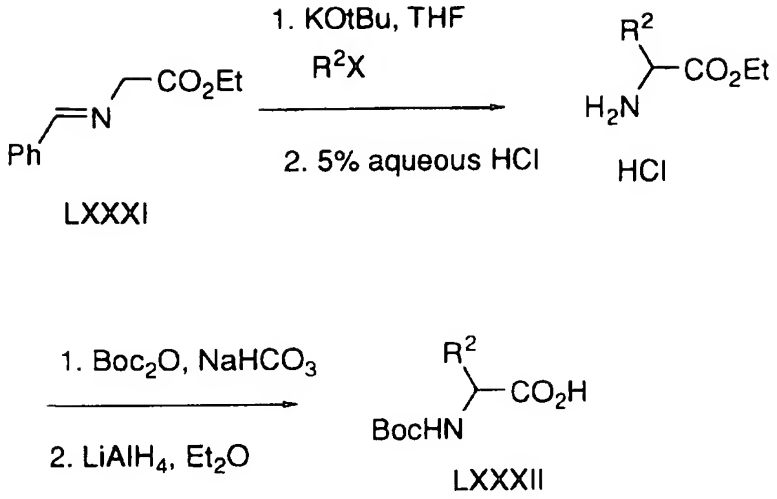
SCHEME 16


sub
1. Boc2O, i-Pr2EtN
2. DIBAL
H2N
HCl
O
O
BocHN
OH
LXXV
OH
sub
Z-NH2
NaBH(OAc)3
ClCH2CH2Cl
BocNH
H
N
Z
LXXVI
HO
sub
Cl
Cl
EtOAc / H2O
NaHCO3
BocNH
N-Z
Cl
O
LXXVII
HO
sub
Cs2CO3
DMF
BocN
N-Z
O
LXXVIII

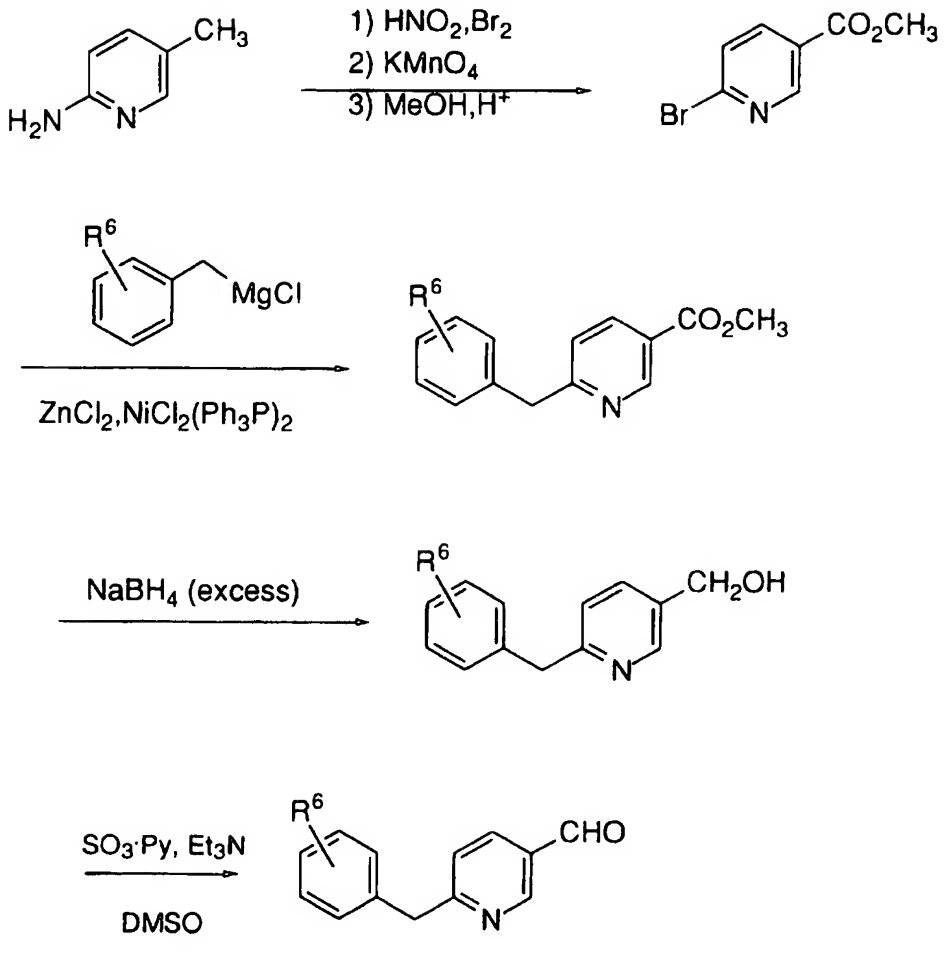
SCHEME 16 (continued)



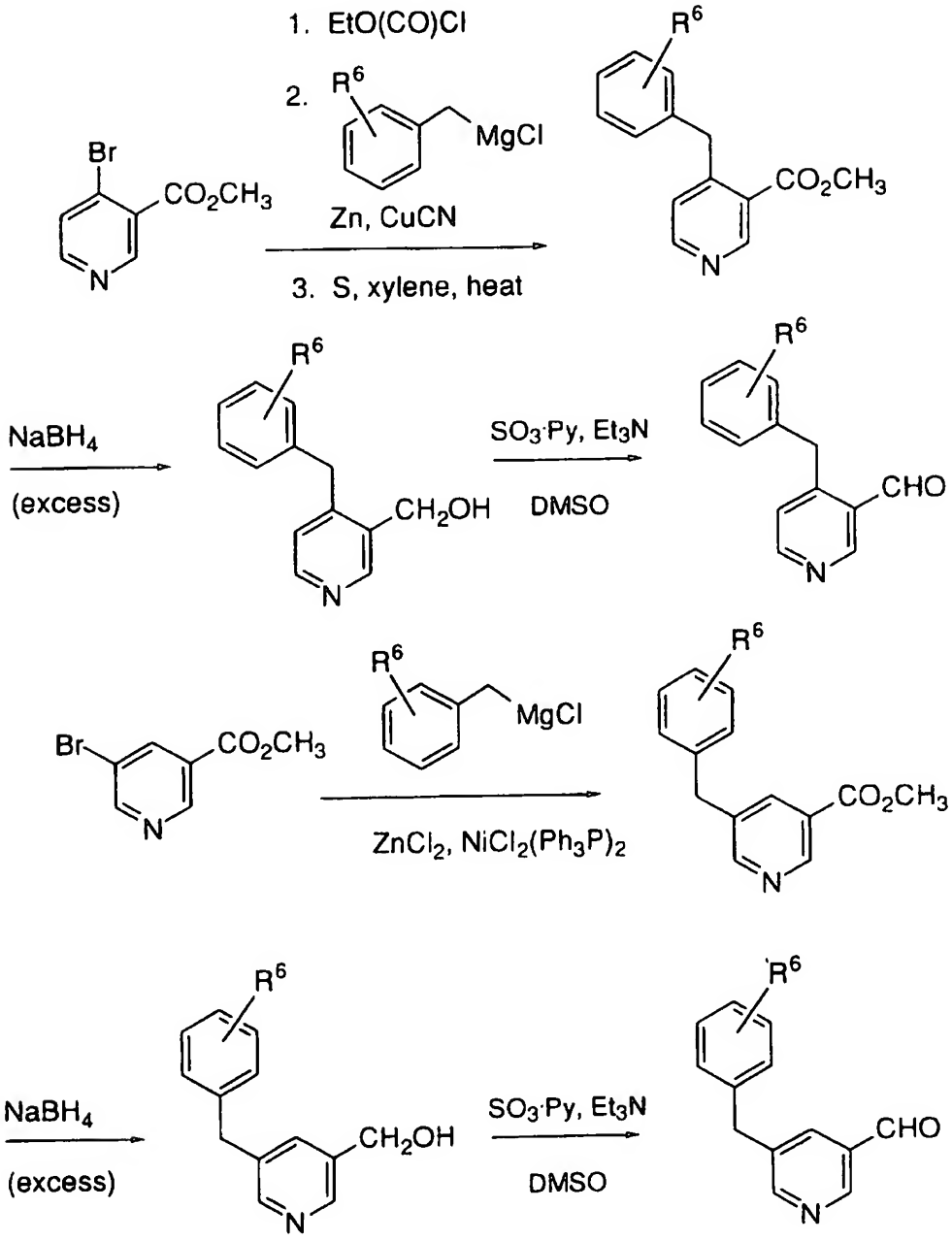
SCHEME 17


1. KOtBu, THF
R2X
2. 5% aqueous HCl
CO2Et
N
Ph
LXXXI
R2
CO2Et
H2N
HCl
1. Boc2O, NaHCO3
2. LiAlH4, Et2O
R2
CO2H
BocHN
LXXXII

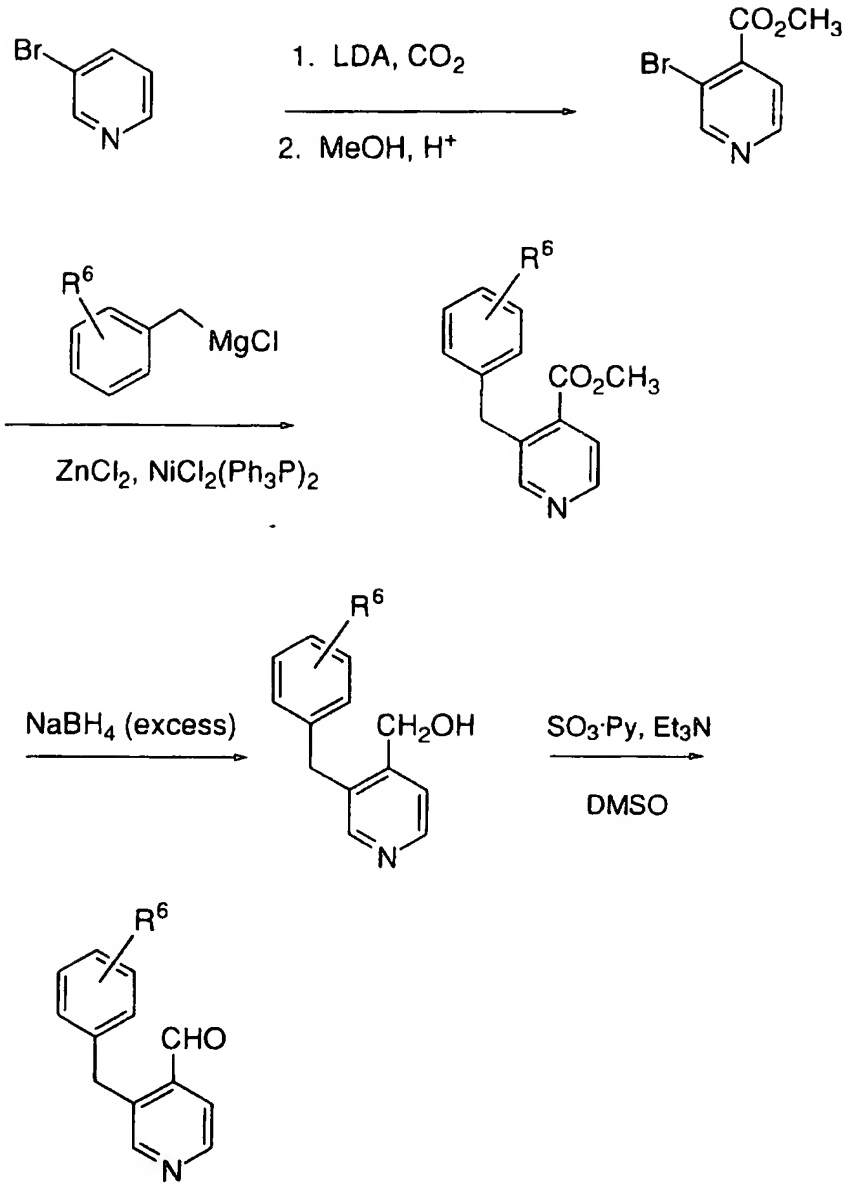
REACTION SCHEME 18



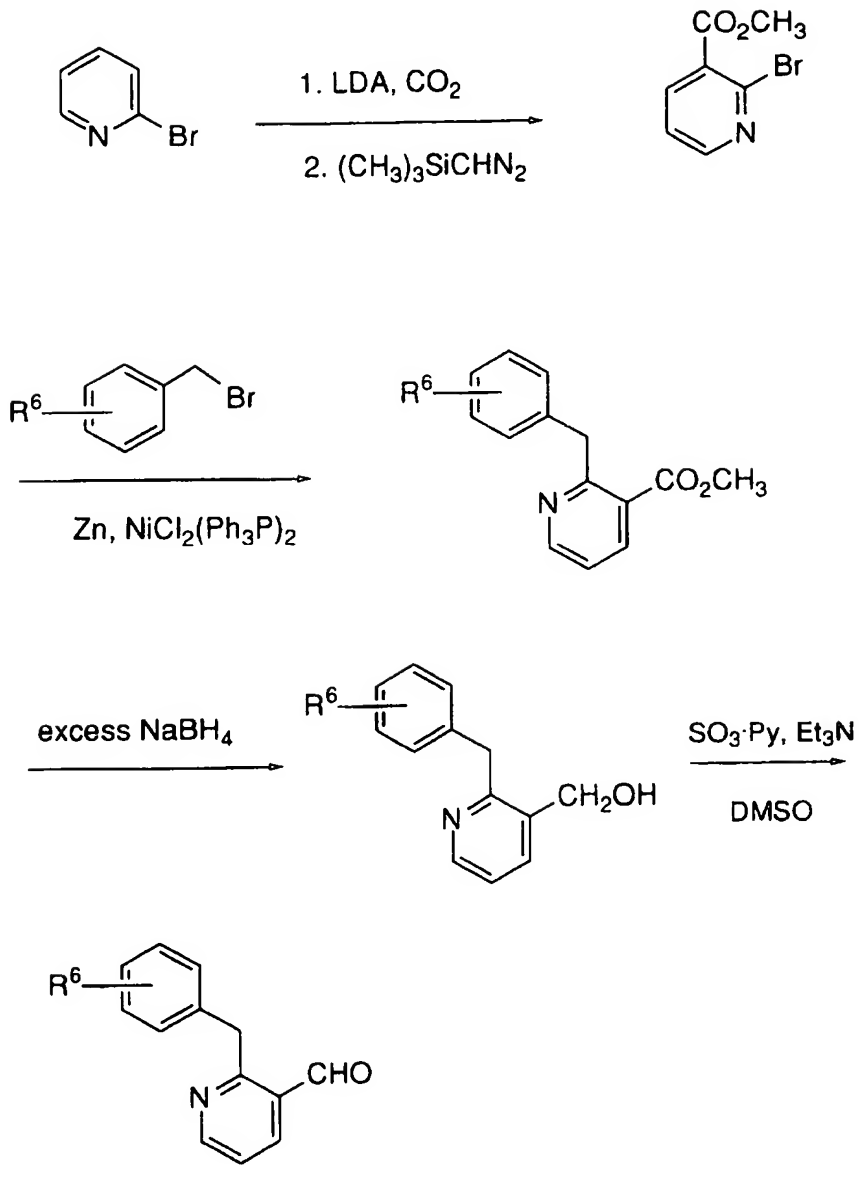
REACTION SCHEME 19



REACTION SCHEME 20



REACTION SCHEME 21



The instant compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer. Examples of the type of cancer which may be treated with the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemias and neurological tumors. Such tumors may arise by mutations in the *ras* genes themselves, mutations in the proteins that can regulate Ras activity (i.e., neurofibromin (NF-1), neu, scr, abl, lck, fyn) or by other mechanisms.

The compounds of the instant invention inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. The instant compounds may also inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55:4575-4580 (1995)). Such anti-angiogenesis properties of the instant compounds may also be useful in the treatment of certain forms of blindness related to retinal vascularization.

The compounds of this invention are also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the compounds of the invention to a mammal in need of such treatment. For example, a component of NF-1 is a benign proliferative disorder.

The instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis delta and related viruses (J.S. Glenn et al. *Science*, 256:1331-1333 (1992).

The compounds of the instant invention are also useful in the prevention of restenosis after percutaneous transluminal coronary angioplasty by inhibiting neointimal formation (C. Indolfi et al. *Nature medicine*, 1:541-545(1995).

The instant compounds may also be useful in the treatment and prevention of polycystic kidney disease (D.L. Schaffner et al.

American Journal of Pathology, 142:1051-1060 (1993) and B. Cowley, Jr. et al.*FASEB Journal*, 2:A3160 (1988)).

The instant compounds may also be useful for the treatment of fungal infections.

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The compounds of the instant invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, the instant compounds may be useful in combination with known anti-cancer and cytotoxic agents. Similarly, the instant compounds may be useful in combination with agents that are effective in the treatment and prevention of NF-1, restinosis, polycystic kidney

disease, infections of hepatitis delta and related viruses and fungal infections.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's blood-stream by local bolus injection.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The compounds of the instant invention are also useful as a component in an assay to rapidly determine the presence and quantity of farnesyl-protein transferase (FPTase) in a composition. Thus the composition to be tested may be divided and the two portions contacted with mixtures which comprise a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine

terminus) and farnesyl pyrophosphate and, in one of the mixtures, a compound of the instant invention. After the assay mixtures are incubated for an sufficient period of time, well known in the art, to allow the FPTase to farnesylate the substrate, the chemical content of the assay mixtures may be determined by well known immunological, radiochemical or chromatographic techniques. Because the compounds of the instant invention are selective inhibitors of FPTase, absence or quantitative reduction of the amount of substrate in the assay mixture without the compound of the instant invention relative to the presence of the unchanged substrate in the assay containing the instant compound is indicative of the presence of FPTase in the composition to be tested.

It would be readily apparent to one of ordinary skill in the art that such an assay as described above would be useful in identifying tissue samples which contain farnesyl-protein transferase and quantitating the enzyme. Thus, potent inhibitor compounds of the instant invention may be used in an active site titration assay to determine the quantity of enzyme in the sample. A series of samples composed of aliquots of a tissue extract containing an unknown amount of farnesyl-protein transferase, an excess amount of a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate are incubated for an appropriate period of time in the presence of varying concentrations of a compound of the instant invention. The concentration of a sufficiently potent inhibitor (i.e., one that has a Ki substantially smaller than the concentration of enzyme in the assay vessel) required to inhibit the enzymatic activity of the sample by 50% is approximately equal to half of the concentration of the enzyme in that particular sample.

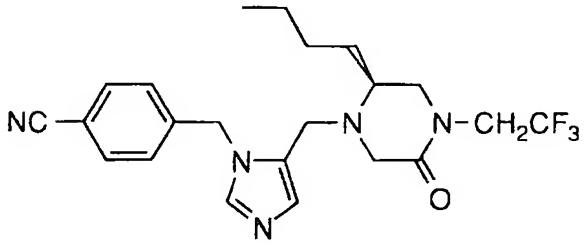
EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species

and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

EXAMPLE 1

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-4-(2,2,2-trifluoroethyl)piperazin-5-one dihydrochloride



L-786,017

Step A: N-Methoxy-N-methyl 2(S)-(*tert*-butoxycarbonylamino)-hexanamide

2(S)-Butoxycarbonylaminohexanoic acid (24.6 g, 0.106 mol), N,O-dimethylhydroxylamine hydrochloride (15.5 g, 0.15 mol), EDC hydrochloride (22.3 g, 0.117 mol) and HOBT (14.3 g, 0.106 mol) were stirred in dry, degassed DMF (300 mL) at 20°C under nitrogen. N-Methylmorpholine was added to obtain pH 7. The reaction was stirred overnight, the DMF distilled under high vacuum, and the residue partitioned between ethyl acetate and 2% potassium hydrogen sulfate. The organic phase was washed with saturated sodium bicarbonate, water, and saturated brine, and dried with magnesium sulfate. The solvent was removed in vacuo to give the title compound.

Step B: 2(S)-(*tert*-Butoxycarbonylamino)hexanal

A mechanically stirred suspension of lithium aluminum hydride (5.00 g, 0.131 mol) in ether (250 mL) was cooled to -45°C under nitrogen. A solution of the product from Step A (28.3 g, 0.103 mol) in ether (125 mL) was added, maintaining the temperature below

-35°C. When the addition was complete, the reaction was warmed to 5°C, then recooled to -45°C. A solution of potassium hydrogen sulfate (27.3 g, 0.200 mol) in water was slowly added, maintaining the temperature below -5°C. After quenching, the reaction was stirred at room temperature for 1h. The mixture was filtered through Celite, the ether evaporated, and the remainder partitioned between ethyl acetate and 2% potassium hydrogen sulfate. After washing with saturated brine, drying over magnesium sulfate and solvent removal, the title compound was obtained.

Step C: N-(2,2,2,-Trifluoroethyl)-2(S)-(*tert*-butoxycarbonylamino)-hexanamine

2,2,2-Trifluoroethylamine hydrochloride (0.407 g, 3.0 mmol) was dissolved in dichloroethane under nitrogen. N-Methyl morpholine (0.330 mL, 3.0 mmol) was added to obtain pH 5-6, and sodium triacetoxyborohydride (0.795 g, 3.75 mmol) was added. A solution of the product from Step B (0.573 g, 2.5 mmol) in dichloroethane (80 mL) was added slowly dropwise at 20°C. The reaction was stirred overnight, then quenched with saturated sodium bicarbonate solution. The aqueous layer was removed, the organic phase washed with saturated brine and dried over magnesium sulfate. The title compound was obtained as an oil.

Step D: 1-*tert*-Butoxycarbonyl-2(S)-*n*-butyl-4-(2,2,2-trifluoroethyl)piperazin-5-one

A solution of the product from Step C (0.590 g, 1.98 mmol) in ethyl acetate (30 mL) was vigorously stirred at 0°C with saturated sodium bicarbonate (30 mL). Chloroacetyl chloride (0.315 mL, 3.96 mmol) was added, and the reaction stirred at 0°C for 1 h. The layers were separated, and the ethyl acetate phase was washed with saturated brine, and dried over magnesium sulfate. The crude product was dissolved in DMF (15 mL) and cooled to 0°C under nitrogen. Cesium carbonate (1.67 g, 5.12 mmol) was added and the reaction stirred 1 h at 0°C, then at room temperature overnight. The reaction

was quenched with amminium chloride, and partitioned between ethyl acetate and water. The organic phase was washed with water, saturated brine, and dried over magnesium sulfate. The title compound was obtained as a colorless oil.

Step E: 1-Triphenylmethyl-4-(hydroxymethyl)imidazole

To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35.0 g, 260 mmol) in 250 mL of dry DMF at room temperature was added triethylamine (90.6 mL, 650 mmol). A white solid precipitated from the solution. Chlorotriphenylmethane (76.1 g, 273 mmol) in 500 mL of DMF was added dropwise. The reaction mixture was stirred for 20 hours, poured over ice, filtered, and washed with ice water. The resulting product was slurried with cold dioxane, filtered, and dried *in vacuo* to provide the titled product as a white solid which was sufficiently pure for use in the next step.

Step F: 1-Triphenylmethyl-4-(acetoxymethyl)-imidazole

Alcohol from Step E (260 mmol, prepared above) was suspended in 500 mL of pyridine. Acetic anhydride (74 mL, 780 mmol) was added dropwise, and the reaction was stirred for 48 hours during which it became homogeneous. The solution was poured into 2 L of EtOAc, washed with water (3 x 1 L), 5% aq. HCl soln. (2 x 1 L), sat. aq. $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. The acetate was isolated as a white powder which was sufficiently pure for use in the next reaction.

Step G: 1-(4-Cyanobenzyl)-5-(acetoxymethyl)-imidazole hydrobromide

A solution of the product from Step F (85.8 g, 225 mmol) and α-bromo-*p*-tolunitrile (50.1 g, 232 mmol) in 500 mL of EtOAc was stirred at 60 °C for 20 hours, during which a pale yellow precipitate formed. The reaction was cooled to room temperature and filtered to provide the solid imidazolium bromide salt. The filtrate was

concentrated *in vacuo* to a volume 200 mL, reheated at 60 °C for two hours, cooled to room temperature, and filtered again. The filtrate was concentrated *in vacuo* to a volume 100 mL, reheated at 60 °C for another two hours, cooled to room temperature, and concentrated *in vacuo* to provide a pale yellow solid. All of the solid material was combined, dissolved in 500 mL of methanol, and warmed to 60 °C. After two hours, the solution was reconcentrated *in vacuo* to provide a white solid which was triturated with hexane to remove soluble materials. Removal of residual solvents *in vacuo* provided the titled product hydrobromide as a white solid which was used in the next step without further purification.

Step H: 1-(4-Cyanobenzyl)-5-(hydroxymethyl)-imidazole

To a solution of the acetate from Step G (50.4 g, 150 mmol) in 1.5 L of 3:1 THF/water at 0 °C was added lithium hydroxide monohydrate (18.9 g, 450 mmol). After one hour, the reaction was concentrated *in vacuo*, diluted with EtOAc (3 L), and washed with water, sat. aq. $NaHCO_3$ and brine. The solution was then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product as a pale yellow fluffy solid which was sufficiently pure for use in the next step without further purification.

Step I: 1-(4-Cyanobenzyl)-5-imidazolecarboxaldehyde

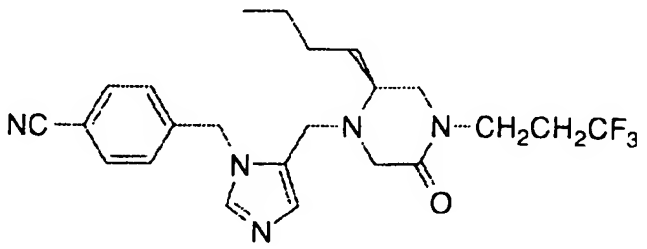
To a solution of the alcohol from Step H (21.5 g, 101 mmol) in 500 mL of DMSO at room temperature was added triethylamine (56 mL, 402 mmol), then SO_3-pyridine complex (40.5 g, 254 mmol). After 45 minutes, the reaction was poured into 2.5 L of EtOAc, washed with water (4 x 1 L) and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the aldehyde as a white powder which was sufficiently pure for use in the next step without further purification.

Step J: 2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-4-(2,2,2-trifluoroethyl)-piperazin-5-one dihydrochloride

A solution of the product from Step D (0.578 g, 1.71 mmol) was stirred in 30% trifluoroacetic acid in methylene chloride for 1 h. The volatiles were removed *in vacuo*, and the residue dissolved in dichloroethane (5 mL). The pH was adjusted to 5-6 with N-methylmorpholine. Sodium triacetoxyborohydride (0.544 g, 2.57 mmol) and 1-(4-cyanobenzyl)imidazolyl-5-carboxaldehyde from Step I (0.361 g, 1.71 mmol) was added. The reaction was stirred overnight at 20°C then poured into saturated sodium bicarbonate solution. The organic phase was washed with saturated brine and dried over magnesium sulfate. The crude product was purified by preparative HPLC on a 40 X 100 mm Waters PrepPak® reverse phase HPLC column (Delta-Pak™ C_{18} 15 µm, 100 Å) using a gradient elution of 25% (0.1% TFA in acetonitrile), 75% (0.1% TFA in water) progressing to 45% (0.1% TFA in acetonitrile), 55% (0.1% TFA in water) over 50 min. Pure fractions were combined, concentrated, and the residue partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate. The purified product was converted to the hydrochloride salt with HCl in dichloromethane. The title compound was obtained as a white solid. FAB ms (m+1) 434. Anal. Calc. for $C_{22}H_{26}F_3N_5O \cdot 2.0$ HCl: C, 52.18; H, 5.57; N, 13.83. Found: C, 52.41; H, 5.60; N, 13.65.

EXAMPLE 2

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-4-[1-(3,3,3-trifluoropropyl)]-piperazin-5-one dihydrochloride



Step A: N-1-(3,3,3-Trifluoropropyl)-2(S)-(*tert*-butoxycarbonylamino)-hexanamine

The title compound is prepared according to the procedure described in Example 1, Step C, except using 1-(3,3,3-trifluoropropyl)amine hydrochloride in place of 2,2,2-trifluoroethylamine hydrochloride.

Step B: 1-*tert*-Butoxycarbonyl-2(S)-*n*-butyl-4-[1-(3,3,3-trifluoropropyl)]piperazin-5-one

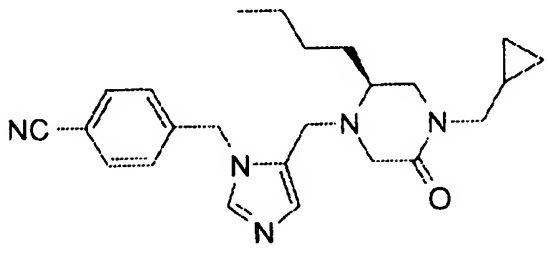
The title compound is prepared according to the procedure described in Example 1, Step D, except using N-1-(3,3,3-trifluoropropyl)-2(S)-(*tert*-butoxycarbonylamino)hexanamine in place of N-(2,2,2,-trifluoroethyl)-2(S)-(*tert*-butoxycarbonylamino)hexanamine.

Step C: 2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-4-[1-(3,3,3-trifluoropropyl)]piperazin-5-one dihydrochloride

The title compound is prepared according to the procedure described in Example 1, Step J, except using 1-*tert*-butoxycarbonyl-2(S)-*n*-butyl-4-[1-(3,3,3-trifluoropropyl)]piperazin-5-one in place of 1-*tert*-butoxycarbonyl-2(S)-*n*-butyl-4-(2,2,2-trifluoroethyl)piperazin-5-one. The purified product is converted to the hydrochloride salt with HCl in dichloromethane.

EXAMPLE 3

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-4-(cyclopropylmethyl)piperazin-5-one dihydrochloride



Step A: N-(Cyclopropylmethyl)-2(S)-(*tert*-butoxycarbonylamino)-hexanamine

The title compound is prepared according to the procedure described in Example 1, Step C, except using cyclopropylmethylamine hydrochloride in place of 2,2,2-trifluoroethylamine hydrochloride.

Step B: 1-*tert*-Butoxycarbonyl-2(S)-*n*-butyl-4-(cyclopropylmethyl)piperazin-5-one

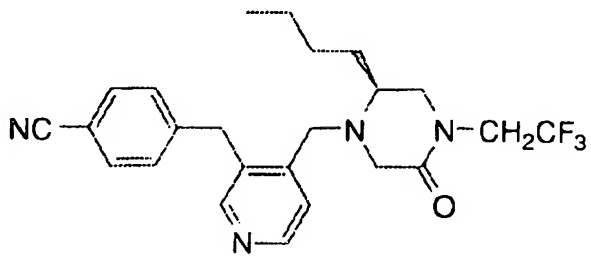
The title compound is prepared according to the procedure described in Example 1, Step D, except using N-(cyclopropylmethyl)-2(S)-(*tert*-butoxycarbonylamino)hexanamine in place of N-(2,2,2,-trifluoroethyl)-2(S)-(*tert*-butoxycarbonylamino)hexanamine.

Step C: 2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-4-(cyclopropylmethyl)piperazin-5-one dihydrochloride

The title compound is prepared according to the procedure described in Example 1, Step J, except using 1-*tert*-butoxycarbonyl-2(S)-*n*-butyl-4-(cyclopropylmethyl)piperazin-5-one in place of 1-*tert*-butoxycarbonyl-2(S)-*n*-butyl-4-(2,2,2-trifluoroethyl)piperazin-5-one to obtain the title compound. The purified product is converted to the dihydrochloride salt with HCl in dichloromethane.

EXAMPLE 4

2(S)-*n*-Butyl-1-[3-(4-cyanobenzyl)pyridin-4-yl]-4-(2,2,2-trifluoroethyl)piperazin-5-one dihydrochloride



Step A: 3-(4-Cyanobenzyl)pyridin-4-carboxylic acid methyl ester

A solution of 4-cyanobenzyl bromide (0.625 g, 3.27 mmol) in dry THF (4 mL) was added slowly over ~3 min to a suspension of activated zinc (dust; 0.250 g) in dry THF (2 mL) at 0°C under an argon atmosphere. The ice-bath was removed and the slurry was stirred at room temperature for a further 30 min. Then 3-bromopyridin-4-carboxylic acid methyl ester (0.540 g. 2.5 mmol) followed by dichlorobis(triphenylphosphine)nickel (II) (50 mg). The resultant reddish-brown mixture was stirred for 3 h at ~40-45°C. The mixture was cooled and distributed between ethyl acetate (100 ml) and 5% aqueous citric acid (50 mL). The organic layer was washed with water (2X50 mL), dried with Na_2SO_4. After evaporation of the solvent the residue was purified on silica gel, eluting with 35% ethyl acetate in hexane to give 0.420 g as a clear gum. FAB ms (M+l) 253.

Step B: 3-(4-Cyanobenzyl)-4-(hydroxymethyl)pyridine

The title compound was obtained by sodium borohydride (300 mg) reduction of the ester from Step A (0.415 g) in methanol (5 mL) at room temperature. After stirring for 4 h the solution was evaporated and the product was purified on silica gel, eluting with 2% methanol in chloroform to give the title compound. FAB ms (M+1) 225.

Step C: 3-(4-Cyanobenzyl)-4-pyridinal

The title compound was obtained by activated manganese dioxide (1.0 g) oxidation of the alcohol from Step B (0.240 g, 1.07 mmol) in dioxane (10 mL) at reflux for 30 min. Filtration and evaporation of the solvent provided title compound, mp 80-83°C.

Step D: 3(S)-*n*-Butyl-1-[3-(4-cyanobenzyl)pyridin-4-yl]-4-(2,2,2-trifluoroethyl)piperazin-5-one dihydrochloride

The title compound is prepared according to the procedure described in Example 1, Step J, except using 3-(4-cyanobenzyl)-4-

pyridinal from Step C in place of 1-(4-cyanobenzyl)imidazolyl-5-carboxaldehyde. The purified product is converted to the dihydrochloride salt with HCl in dichloromethane.

EXAMPLE 5

In vitro inhibition of ras farnesyl transferase

Assays of farnesyl-protein transferase. Partially purified bovine FPTase and Ras peptides (Ras-CVLS, Ras-CVIM and Ras-CAIL) were prepared as described by Schaber et al., J. Biol. Chem. 265:14701-14704 (1990), Pompliano, et al., Biochemistry 31:3800 (1992) and Gibbs et al., PNAS U.S.A. 86:6630-6634 (1989), respectively. Bovine FPTase was assayed in a volume of 100 µl containing 100 mM *N*-(2-hydroxy ethyl) piperazine-*N'*-(2-ethane sulfonic acid) (HEPES), pH 7.4, 5 mM $MgCl_2$, 5 mM dithiothreitol (DTT), 100 mM [^{3}H]-farnesyl diphosphate ([^{3}H]-FPP; 740 CBq/mmol, New England Nuclear), 650 nM Ras-CVLS and 10 µg/ml FPTase at 31°C for 60 min. Reactions were initiated with FPTase and stopped with 1 ml of 1.0 M HCL in ethanol. Precipitates were collected onto filter-mats using a TomTec Mach II cell harvestor, washed with 100% ethanol, dried and counted in an LKB β-plate counter. The assay was linear with respect to both substrates, FPTase levels and time; less than 10% of the [^{3}H]-FPP was utilized during the reaction period. Purified compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and were diluted 20-fold into the assay. Percentage inhibition is measured by the amount of incorporation of radioactivity in the presence of the test compound when compared to the amount of incorporation in the absence of the test compound.

Human FPTase was prepared as described by Omer et al., Biochemistry 32:5167-5176 (1993). Human FPTase activity was assayed as described above with the exception that 0.1% (w/v) polyethylene glycol 20,000, 10 µM $ZnCl_2$ and 100 nM Ras-CVIM were added to the reaction mixture. Reactions were performed for 30 min.,

stopped with 100 µl of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed as described above for the bovine enzyme.

The compounds of the instant invention described in the above Examples and in the Tables hereinafter were tested for inhibitory activity against human FPTase by the assay described above and were found to have IC_{50} of ≤50 µM.

EXAMPLE 6

In vivo ras farnesylation assay

The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The assay is performed essentially as described in DeClue, J.E. et al., Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluency are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemeted with 10% regular DMEM, 2% fetal bovine serum and 400 mCi[^{35}S]methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM $MgCl_2$/1mM DTT/10 mg/ml aprotinen/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Aliquots of lysates containing equal numbers of acid-precipitable counts are bought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. et al., J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 ml of a 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 nM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100.0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to

farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

EXAMPLE 7

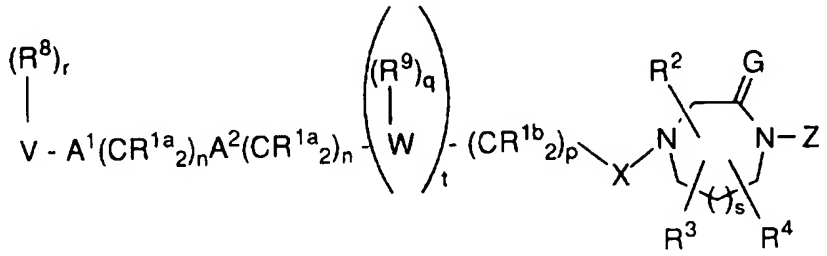
In vivo growth inhibition assay

To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a v-*ras*, v-*raf*, or v-*mos* oncogene is tested. Cells transformed by v-Raf and v-Mos maybe included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

Rat 1 cells transformed with either v-ras, v-raf, or v-mos are seeded at a density of 1 x 10^4 cells per plate (35 mm in diameter) in a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the instant compound (dissolved in methanol at 1000 times the final concentration used in the assay). The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photomicrographs are taken 16 days after the cultures are seeded and comparisons are made.

WHAT IS CLAIMED IS:

1. A compound which inhibits farnesyl-protein transferase of the formula A:



A

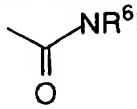
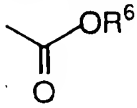
wherein:

R^{1a} and R^{1b} are independently selected from:

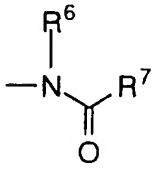
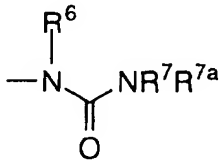
a) hydrogen,

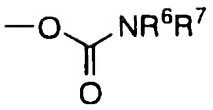
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $CN(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

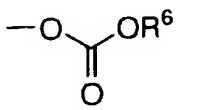
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

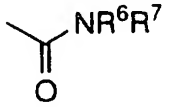
R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl,  or  , unsubstituted or substituted heterocycle,

wherein the substituted group is substituted with one or more of:

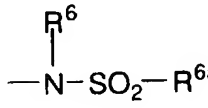
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
   e) CN,
   f) aryl or heteroaryl,
   g) perfluoro-C_{1-4} alkyl,
   h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},
5) $-NR^6R^7$,
6)  ,
7)  ,

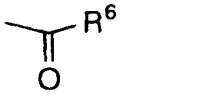
8)  ,

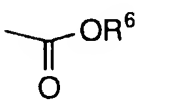
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  ,

14)  ,

15) N_3,

16) F, or

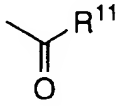
17) perfluoro-C_{1-4}-alkyl; or

R^2 and R^3 are attached to the same C atom and are combined to form -$(CH_2)_u$- wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -$N(COR^{10})$- ;

R^4 is selected from H and CH_3;

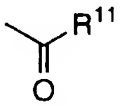
and any two of R^2, R^3 and R^4 are optionally attached to the same carbon atom;

R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring;
R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$;

R^8 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-,

$R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

G is H_2 or O;

V is selected from:

a) hydrogen,

b) heterocycle.

c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

X is $-CH_2-$, $-C(=O)-$, or $-S(=O)_m-$;

Z is unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:
a) C_1-4 alkoxy,
b) NR^6R^7,
c) C_3-6 cycloalkyl,
d) $-NR^6C(O)R^7$,
e) HO,
f) $-S(O)_mR^{6a}$,
g) halogen, or
h) perfluoroalkyl;

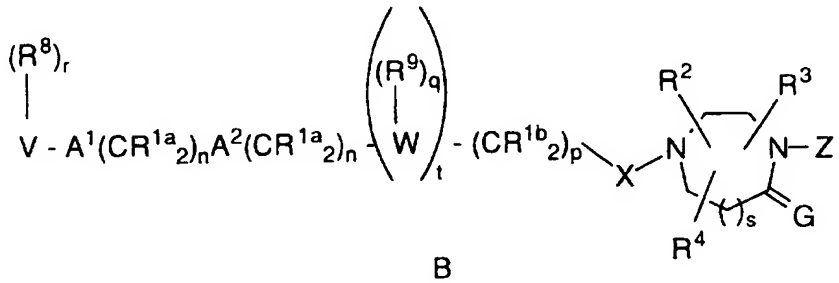
m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 1 or 2;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 0 or 1;
t is 0 or 1; and
u is 4 or 5;

provided that when G is H_2 and W is imidazolyl, then the substitutent $(R^8)_r$- V - $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ - is not H and

provided that when X is -C(=O)-, or -S(=O)m-, then t is 1 and the substitutent $(R^8)_r$- V - $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ - is not H;

or a pharmaceutically acceptable salt thereof.

2. A compound which inhibits farnesyl-protein transferase of the formula B:



B

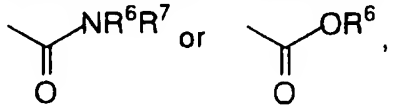
wherein:

R^{1a} and R^{1b} are independently selected from:

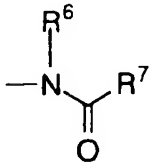
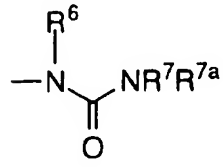
a) hydrogen,

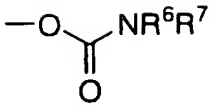
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

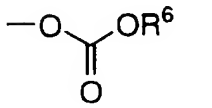
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

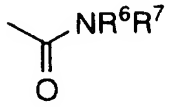
R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl,  , unsubstituted or substituted heterocycle,

wherein the substituted group is substituted with one or more of:

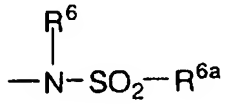
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
   e) CN,
   f) aryl or heteroaryl,
   g) perfluoro-C_{1-4} alkyl,
   h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},
5)  ,
6)  ,
7)  ,

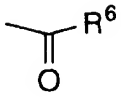
8)  ,

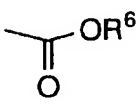
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  ,

14)  ,

15) N_3,

16) F, or

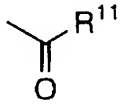
17) perfluoro-C_{1-4}-alkyl; or

R^2 and R^3 are attached to the same C atom and are combined to form -$(CH_2)_u$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -$N(COR^{10})$- ;

R^4 is selected from H and CH_3;

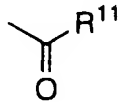
and any two of R^2, R^3 and R^4 are optionally attached to the same carbon atom;

R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e) 
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring;
R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e) 
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$;

R^8 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-,

$R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

G is O;

V is selected from:

a) hydrogen,

b) heterocycle,

c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

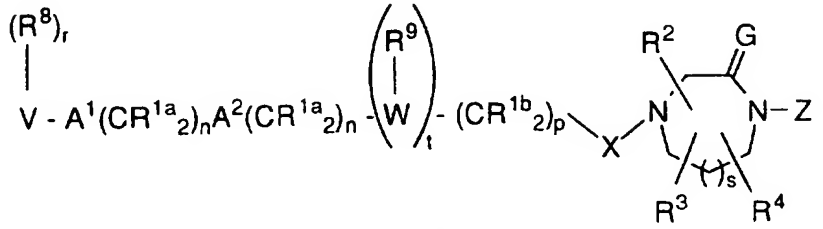
X is $-CH_2-$, $-C(=O)-$, or $-S(=O)_m-$;

Z is unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:
a) C_{1-4} alkoxy,
b) NR^6R^7,
c) C_{3-6} cycloalkyl,
d) $-NR^6C(O)R^7$,
e) HO,
f) $-S(O)_mR^{6a}$,
g) halogen, or
h) perfluoroalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 1 or 2;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 1;
t is 0 or 1; and
u is 4 or 5;

or a pharmaceutically acceptable salt thereof.

3. The compound according to Claim 1 of the formula A:



A

wherein:

R^{1a} is independently selected from: hydrogen or C_1-C_6 alkyl;

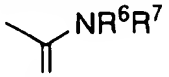
R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or C_2-C_6 alkenyl,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$- and -$N(R^{10})_2$;

R^3 and R^4 are independently selected from H and CH_3;

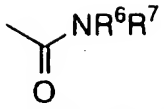
R^2 is H;  or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,

2) heterocycle,

3) OR^6,

4) SR^{6a}, SO_2R^{6a}, or

5)  ;

and any two of R^2, R^3, R^4, and R^5 are optionally attached to the same carbon atom;

R^6, R^7 and R^{7a} are independently selected from:
H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:
a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^{6a} is selected from:
C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:
a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^8 is independently selected from:
a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^9 is selected from:
a) hydrogen,
b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2,

$(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, O, -N(R^{10})-, or S(O)m;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is S(O)m and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)m;

G is H_2 or O;

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

X is $-CH_2-$ or $-C(=O)-$;

Z is unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:

a) C_{1-4} alkoxy,
b) NR^6R^7,
c) C_{3-6} cycloalkyl,
d) $-NR^6C(O)R^7$,
e) HO,
f) $-S(O)_mR^{6a}$,
g) halogen, or
h) perfluoroalkyl;

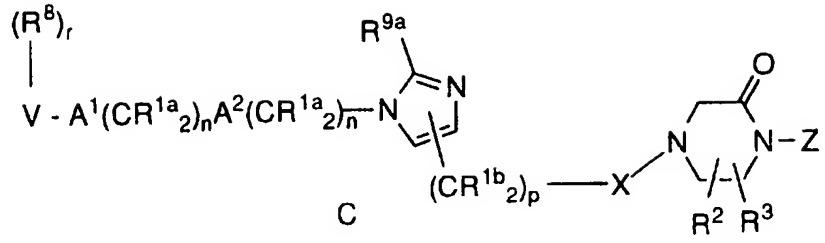
m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 0 or 1;
t is 0 or 1; and
u is 4 or 5;

provided that when G is H_2 and W is imidazolyl, then the substitutent $(R^8)_r$- V - $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ - is not H and

provided that when X is $-C(=O)-$, or $-S(=O)_m-$, then t is 1 and the substitutent $(R^8)_r$- V - $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ - is not H;

or a pharmaceutically acceptable salt thereof.

4. The compound according to Claim 1 of the formula C:



wherein:

R^{1a} is selected from: hydrogen or C_1-C_6 alkyl;

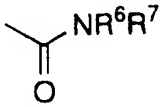
R^{1b} is independently selected from:

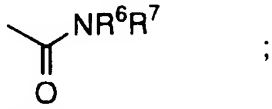
a) hydrogen,

b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from H and CH_3;

R^2 is selected from H;  or C_1-$_5$ alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^6,
4) SR^{6a}, SO_2R^{7a}, or
5) 

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from:
H; C_1-$_4$ alkyl, C_3-$_6$ cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) C_1-$_4$ alkoxy,

b) halogen, or
c) aryl or heterocycle;

R^{6a} is selected from:
C_{1-4} alkyl or C_{3-6} cycloalkyl,
unsubstituted or substituted with:
a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^8 is independently selected from:
a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, O, -$N(R^{10})$-, or $S(O)_m$;

V is selected from:
a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is S(O)m and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)m;

X is $-CH_2-$ or -C(=O)-;

Z is unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:

a) C_{1-4} alkoxy,

b) NR^6R^7,

c) C_{3-6} cycloalkyl,

d) $-NR^6C(O)R^7$,

e) HO,

f) $-S(O)_mR^{6a}$,

g) halogen, or

h) perfluoroalkyl;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

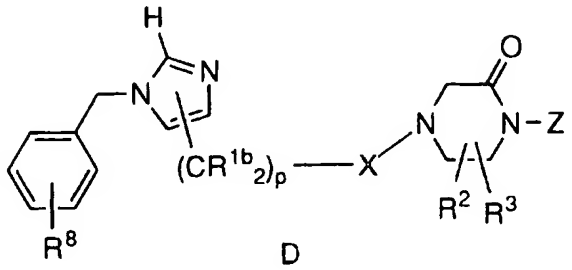
p is 0, 1, 2, 3 or 4; and

r is 0 to 5, provided that r is 0 when V is hydrogen;

provided that when X is -C(=O)-, or $-S(=O)_m-$, then t is 1 and the substitutent $(R^8)_r$- V - $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ - is not H;

or a pharmaceutically acceptable salt thereof.

5. The compound according to Claim 1 of the formula D:



D

wherein:

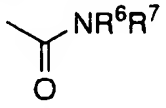
R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^3 is selected from H and CH_3;

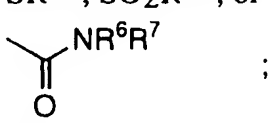
R^2 is selected from H;  or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,

2) heterocycle,

3) OR^6,

4) SR^{6a}, SO_2R^{7a}, or

5)  ;

and R^2 and R^3 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from:
H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle,
unsubstituted or substituted with:
a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^{6a} is selected from:
C_{1-4} alkyl or C_{3-6} cycloalkyl,
unsubstituted or substituted with:
a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^8 is independently selected from:
a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

X is $-CH_2-$ or $-C(=O)-$:

Z is unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6

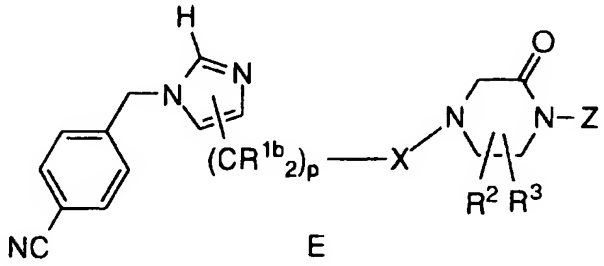
cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:

a) C_{1-4} alkoxy,
b) NR^6R^7,
c) C_{3-6} cycloalkyl,
d) $-NR^6C(O)R^7$,
e) HO,
f) $-S(O)_mR^{6a}$,
g) halogen, or
h) perfluoroalkyl;

m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

6. The compound according to Claim 1 of the formula E:



E

wherein:

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, cycloalkyl, $R^{10}O-$, $-N(R^{10})_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^2 and R^3 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

X is -CH_2- or -C(=O)-;

Z is unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:

a) C_{1-4} alkoxy,
b) NR^6R^7,
c) C_{3-6} cycloalkyl,
d) -$NR^6C(O)R^7$,
e) HO,
f) -$S(O)_mR^{6a}$,
g) halogen, or
h) perfluoroalkyl;

m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

7. A compound which inhibits farnesyl-protein transferase which is:

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-4-(2,2,2-trifluoroethyl)piperazin-5-one dihydrochloride

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-4-[1-(3,3,3-trifluoropropyl)]-piperazin-5-one dihydrochloride

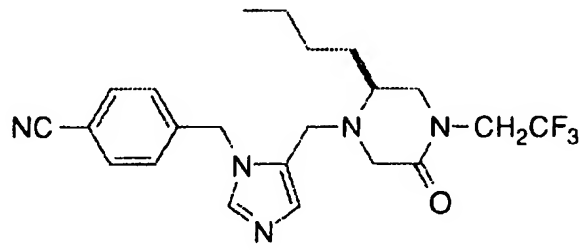
2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-4-(cyclopropylmethyl)piperazin-5-one dihydrochloride and

2(S)-*n*-Butyl-1-[3-(4-cyanobenzyl)pyridin-4-yl]-4-(2,2,2-trifluoroethyl)piperazin-5-one dihydrochloride

or a pharmaceutically acceptable salt or optical isomer thereof.

8. The compound according to Claim 7 which is:

2(S)-*n*-Butyl-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-4-(2,2,2-trifluoroethyl)piperazin-5-one dihydrochloride



or a pharmaceutically acceptable salt or optical isomer thereof.

9. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

10. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 2.

11. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 3.

12. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 7.

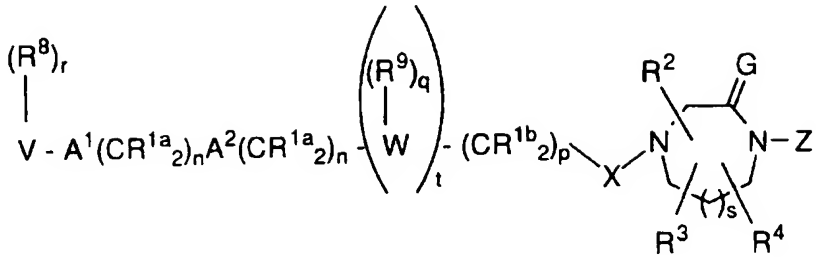
13. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

14. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

15. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 11.

16. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.

17. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of the formula A:



A

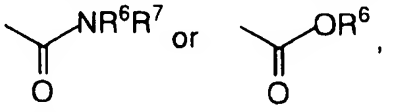
wherein:

R^{1a} and R^{1b} are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $CN(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl,  unsubstituted or substituted heterocycle,

wherein the substituted group is substituted with one or more of:

1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,

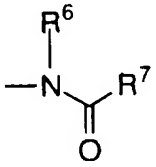
d) halogen,
e) CN,
f) aryl or heteroaryl,
g) perfluoro-C_{1-4} alkyl,
h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},

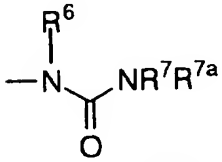
2) C_{3-6} cycloalkyl,

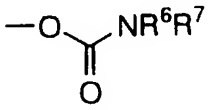
3) OR^6,

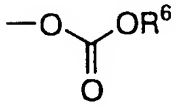
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},

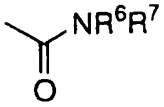
5) $-NR^6R^7$,

6)  ,

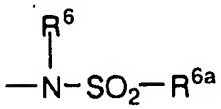
7)  ,

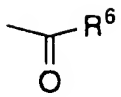
8)  ,

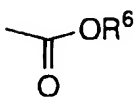
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  ,

14)  ,

15) N_3,

16) F, or

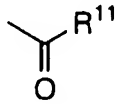
17) perfluoro-C_{1-4}-alkyl; or

R^2 and R^3 are attached to the same C atom and are combined to form -$(CH_2)_u$- wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -$N(COR^{10})$- ;

R^4 is selected from H and CH_3;

and any two of R^2, R^3 and R^4 are optionally attached to the same carbon atom;

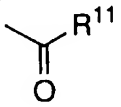
R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring;

R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e) 
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$;

R^8 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,
b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

G is H_2;

V is selected from:

a) hydrogen,
b) heterocycle,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is imidazolyl;

X is -CH_2-, -C(=O)-, or -$S(=O)_m$-;

Z is unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and

substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:

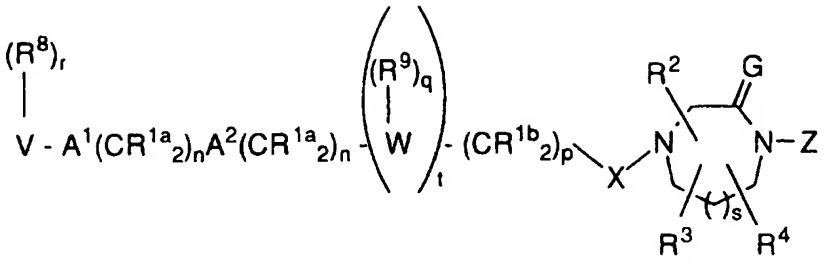
a) C_{1-4} alkoxy,
b) NR^6R^7,
c) C_{3-6} cycloalkyl,
d) $-NR^6C(O)R^7$,
e) HO,
f) $-S(O)_mR^{6a}$,
g) halogen, or
h) perfluoroalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 1 or 2;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 0 or 1;
t is 1; and
u is 4 or 5;

provided that the substitutent $(R^8)_r$- V - $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ - is H;

or a pharmaceutically acceptable salt thereof.

18. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of the formula:



A

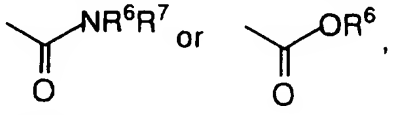
wherein:

R^{1a} and R^{1b} are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $CN(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl,  unsubstituted or substituted heterocycle,

wherein the substituted group is substituted with one or more of:

1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,

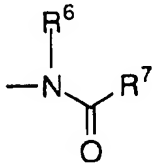
d) halogen,
e) CN,
f) aryl or heteroaryl,
g) perfluoro-C_{1-4} alkyl,
h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},

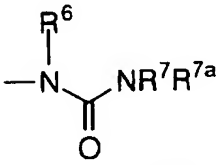
2) C_{3-6} cycloalkyl,

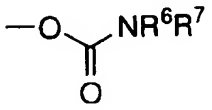
3) OR^6,

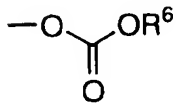
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},

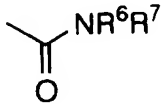
5) $-NR^6R^7$,

6)  ,

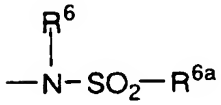
7)  ,

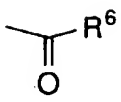
8)  ,

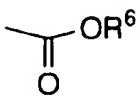
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  ,

14)  ,

15) N_3,

16) F, or

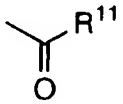
17) perfluoro-C_{1-4}-alkyl; or

R^2 and R^3 are attached to the same C atom and are combined to form -$(CH_2)_u$- wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -$N(COR^{10})$- ;

R^4 is selected from H and CH_3;

and any two of R^2, R^3 and R^4 are optionally attached to the same carbon atom;

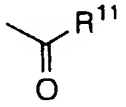
R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring;

R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e) 
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$;

R^8 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,
b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

G is H_2 or O;

V is selected from:

a) hydrogen,
b) heterocycle,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

X is --C(=O)-, or -$S(=O)_m$-;

Z is unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and

substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:

a) C_{1-4} alkoxy,
b) NR^6R^7,
c) C_{3-6} cycloalkyl,
d) $-NR^6C(O)R^7$,
e) HO,
f) $-S(O)_mR^{6a}$,
g) halogen, or
h) perfluoroalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 1 or 2;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 0 or 1;
t is 0 or 1; and
u is 4 or 5;

provided that if t is 1, then the substitutent $(R^8)_r$- V - $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ - is H;

or a pharmaceutically acceptable salt thereof.

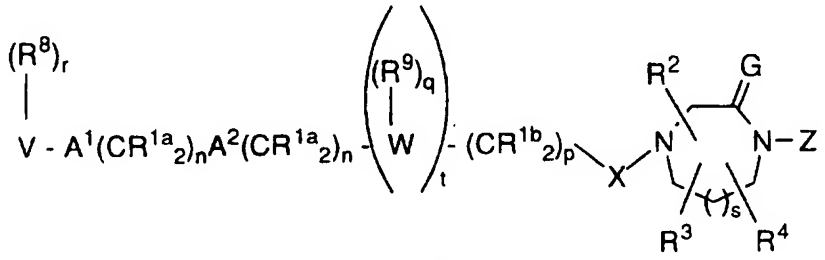
19. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

20. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

21. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 11.

22. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 12.

23. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of the formula A:



A

wherein:

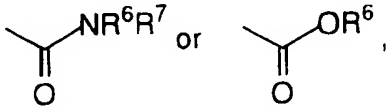
R^{1a} and R^{1b} are independently selected from:

a) hydrogen,

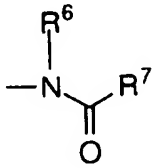
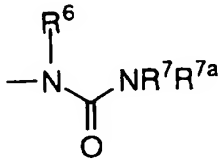
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $CN(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

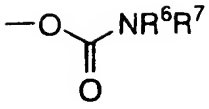
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-

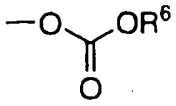
$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

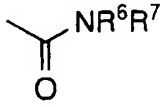
R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl,  , unsubstituted or substituted heterocycle,

wherein the substituted group is substituted with one or more of:

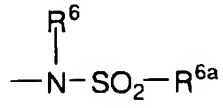
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
   e) CN,
   f) aryl or heteroaryl,
   g) perfluoro-C_{1-4} alkyl,
   h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},
5)  ,
6)  ,
7)  ,

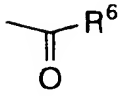
8)  ,

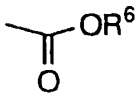
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  ,

14)  ,

15) N_3,

16) F, or

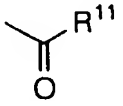
17) perfluoro-C_{1-4}-alkyl; or

R^2 and R^3 are attached to the same C atom and are combined to form -$(CH_2)_u$- wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -$N(COR^{10})$- ;

R^4 is selected from H and CH_3;

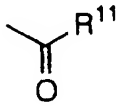
and any two of R^2, R^3 and R^4 are optionally attached to the same carbon atom;

R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e) 
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring;
R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e) 
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$;

R^8 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)m$-,

$R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

G is H_2;

V is selected from:

a) hydrogen,

b) heterocycle,

c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is imidazolyl;

X is $-CH_2-$, $-C(=O)-$, or $-S(=O)_m-$;

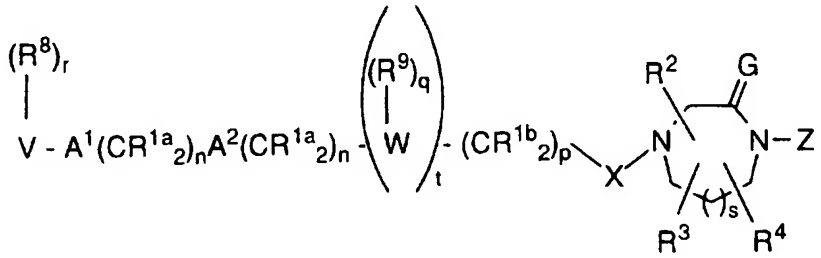
Z is unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:
a) C_{1-4} alkoxy,
b) NR^6R^7,
c) C_{3-6} cycloalkyl,
d) $-NR^6C(O)R^7$,
e) HO,
f) $-S(O)_mR^{6a}$,
g) halogen, or
h) perfluoroalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 1 or 2;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 0 or 1;
t is 1: and
u is 4 or 5;

provided that the substitutent $(R^8)_r$- V - $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ - is H;

or a pharmaceutically acceptable salt thereof.

24. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of the formula:



A

wherein:

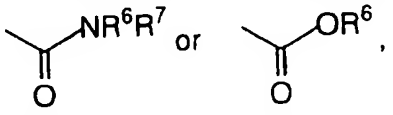
R^{1a} and R^{1b} are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $CN(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

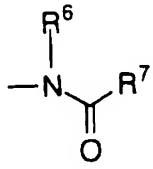
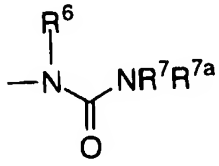
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

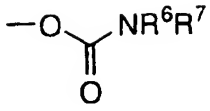
R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl,

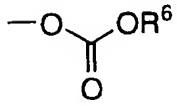


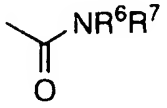
unsubstituted or substituted heterocycle,

wherein the substituted group is substituted with one or more of:

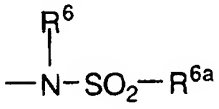
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
   e) CN,
   f) aryl or heteroaryl,
   g) perfluoro-C_{1-4} alkyl,
   h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},
5)  ,
6)  ,
7)  ,

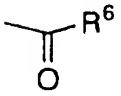
8)  ,

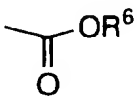
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  ,

14)  ,

15) N_3,

16) F, or

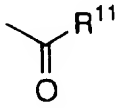
17) perfluoro-C_{1-4}-alkyl; or

R^2 and R^3 are attached to the same C atom and are combined to form $-(CH_2)_u-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and $-N(COR^{10})-$;

R^4 is selected from H and CH_3;

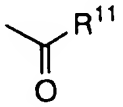
and any two of R^2, R^3 and R^4 are optionally attached to the same carbon atom;

R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring;
R^7 and R^{7a} may be joined in a ring;

R^{6a} is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,
e)  ,
f) $-SO_2R^{11}$, or
g) $N(R^{10})_2$;

R^8 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)m$-,

$R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) alkenyl, alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^{11} is independently selected from C_1-C_6 alkyl and aryl;.

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^{10}$-, -$NR^{10}C(O)$-, O, -$N(R^{10})$-, -$S(O)_2N(R^{10})$-, -$N(R^{10})S(O)_2$-, or $S(O)_m$;

G is H_2 or O;

V is selected from:

a) hydrogen,

b) heterocycle,

c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle;

X is --C(=O)-, or $-S(=O)_m-$;

Z is unsubstituted C_1-C_6 alkyl, substituted C_1-C_6 alkyl, unsubstituted C_3-C_6 cycloalkyl or substituted C_3-C_6 cycloalkyl,wherein the substituted C_1-C_6 alkyl and substituted C_3-C_6 cycloalkyl is substituted with one or two of the following:
a) C_1-4 alkoxy,
b) NR^6R^7,
c) C_3-6 cycloalkyl,
d) $-NR^6C(O)R^7$,
e) HO,
f) $-S(O)_mR^{6a}$,
g) halogen, or
h) perfluoroalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 1 or 2;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 0 or 1;
t is 0 or 1; and
u is 4 or 5;

provided that if t is 1, then the substitutent $(R^8)_r$- V - $A^1(CR^{1a}{}_2)_nA^2(CR^{1a}{}_2)_n$ - is H;

or a pharmaceutically acceptable salt thereof.

25. A method for treating neurofibromin benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

26. A method for treating blindness related to retinal vascularization which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

27. A method for treating infections from hepatitis delta and related viruses which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

28. A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

29. A method for treating polycystic kidney disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05144

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/495; C07D 403/06
US CL : 514/255; 544/370
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/255; 544/370

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Structure Search - file Registry and CAPlus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,835,154 A (FINKLESTEIN ET AL) 30 March 1989 (30/03/89).	1-29
A	US 5,478,934 A (YUAN ET AL) 26 December 1995 (26/12/95).	1-29
A	US 5,128,355 A (CARINI ET AL) 07 July 1992 (07/06/92).	1-29
A	US 5,219,856 A (OLSON) 15 June 1993 (15/06/93).	1-29
A, P	WO 96/16057 A1 (NEUROGEN CORPORATION) 30 May 1996 (30/05/96).	1-29
A	US 3,915,981 A (NAKANISHI ET AL) 28 October 1975 (28/10/75).	1-29

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 22 MAY 1997	Date of mailing of the international search report 24 JUN 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RICHARD S. MYERS, JR. Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*